Nutrition and growth in children with chronic renal insufficiency

By

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Volume I

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Abstract

Practical joint dietetic/ medical guidelines are required for children with differing levels of severity of chronic renal insufficiency (CRI). This thesis describes the current dietetic/ medical package of care provided within a specialised paediatric renal unit, and provides an insight into considerations for future clinical guidelines.

Children were grouped at baseline following [^{51}Cr]-labelled EDTA glomerular filtration rate (GFR, ml/min/1.73m^2) estimations, into 'normal' kidney function [GFR > 75, mean 106 (SD 19.5), n=58], providing baseline data only, mild (GFR 51-75, n=27), moderate (GFR 25-50, n=21) and severe (GFR < 25, n=19) CRI. Those with CRI were followed for two years and 51 children completed the study (19 mild, 19 moderate, 13 severe CRI). Baseline and 6 monthly measurements of anthropometry, blood pressure, laboratory investigations and yearly dietary intakes (3-day semi-quantitative diaries) were obtained. EDTA GFR's were compared to estimations of GFR using serum cystatin C and plasma creatinine/ height concentrations.

Amongst the findings, mean standard deviation scores (SDS) for all anthropometric markers deteriorated with worsening renal function at baseline, from mean SDS for weight, height, body mass index and mid upper arm circumference in 'normal' children of 0.28 (SD 1.0), 0.19 (SD 1.0), 0.21 (SD 1.1) and 0.39 (SD 1.0) respectively, to values of –1.32 (SD 1.0), -1.55 (SD 1.1), -0.44 (SD 1.1) and –0.58 (SD 0.9) in severe CRI. Over two years, mean height SDS significantly increased in children with severe CRI ($p=0.003$) and was maintained in mild and moderate CRI, despite deterioration in renal function. Correlation between changes in energy intake and height SDS was observed in severe CRI ($r^2=0.5$, $p=0.001$). From individual observations and correlation, higher phosphate and sodium intakes appeared to be associated with greater deterioration in estimated GFR in children with mild CRI. An inverse correlation between calcium intake and plasma parathyroid hormone was observed in severe CRI ($r^2=0.27$, $p=0.065$).

Disturbances in nutritional intakes, bone biochemistry and growth occurred early in the course of CRI and deterioration in renal function, as determined by estimated GFR, was greatest in those with mild CRI. Regular joint dietetic/ medical intervention is likely to be beneficial in children with mild and moderate CRI, in addition to those with more severe CRI, to both correct initial disturbances and reduce the chances of progression.

Publications

1. Norman L.J., Coleman J.E., Macdonald I.A., Tomsett A.M. & Watson A.R., 2000. Nutrition and growth in relation to severity of renal disease in children. *Pediatr Nephrol*; **15**: 259-265.

2. Norman L., Coleman J., Evans J., Tomsett M. & Watson A., 1999. Nutrition and growth in relation to severity of chronic renal insufficiency in children. *J Ren Nutr*; **9 (4)**: 229 (abstract).

Presentations

1. *12th British Renal Symposium, 9th British Paediatric Renal Symposium, Manchester, UK, June 2001 (poster presentation)*
   Norman L.J., Whitehead A., Price C.P., Macdonald I.A. & Watson A.R., 2001. Cystatin C as a marker of early renal impairment – clinical implications.

2. *10th International Congress on Nutrition and Metabolism in Renal Disease, Lyon, France, July 2000 (poster presentation)*
   Norman L.J., Coleman J.E., Macdonald I.A., Tomsett A.M. & Watson A.R., 2000. Nutrition and growth in relation to severity of renal disease in children.

3. *49th Annual Meeting of the National Kidney Foundation for the Council of Renal Nutrition, Miami, USA, November 1999 (oral presentation)*
   Norman L., Coleman J., Evans J., Tomsett M. & Watson A., 1999. Nutrition and growth in relation to severity of chronic renal insufficiency in children.

Declaration

I confirm that the entirety of this thesis is my own work, unless otherwise stated. The clinical supervision of patients was conducted by either of the two consultant paediatric nephrologists, the majority of dietetic supervision was conducted by me, although a small proportion of patients were principally under the care of my dietetic colleague. Weight, height and blood pressure were measured by trained out-patient nursing staff, and biochemical variables (apart from cystatin C, measured at St Bartholomew's and The Royal London School of Medicine and Dentistry, London) were measured in the hospital's clinical chemistry and haematology laboratories.

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Finally, on a more personal note, I wish to mention my fiancé Michael Waddell, who has supported me steadfastly throughout my year of writing up, has kept me fed and watered, and, I am sure, will continue to be a great support to me in the future.

Abbreviations

Abbreviation	Full Term
α1-AG	Alpha-1 acid glycoprotein
ACEI	Angiotensin Converting Enzyme Inhibitor
AIPRI	ACE Inhibition in Progressive Renal Insufficiency study
ANOVA	Analysis Of Variance
BCG	Bromocresol Green
BCP	Bromocresol Purple
BIA	Bioelectrical Impedence Analysis
BMI	Body Mass Index
BMR	Basal Metabolic Rate
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CASH	Consensus Action on Salt and Hypertension group
CI	Confidence Interval
COMA	Committee on Medical Aspects
^{51}Cr-EDTA	Radio-labelled Chromium-Edetic Acid
CRF	Chronic Renal Failure
CRI	Chronic Renal Insufficiency
CRP	C-Reactive Protein
DASH	Dietary Approaches to Stop Hypertension study
DBP	Diastolic Blood Pressure
DEXA	Dual Energy X-ray Absorptiometry
DoH	Department of Health
DRV	Dietary Reference Value
EAA	Essential Amino Acids
EAR	Estimated Average Requirement
EI	Energy Intake
EIA	Electro Immunoassay
EPO	Erythropoietin
ESRD	End Stage Renal Disease
GFR	Glomerular Filtration Rate
GFRD	Growth Failure in children with Renal Diseases study
GH	Growth Hormone

Abbreviation	Full Term
Hb	Haemoglobin
HBV	High Biological Value
HDL	High Density Lipoprotein
HTGL	Hepatic Triglyceride Lipase
HUS	Haemolytic Uraemic Syndrome
IBW	Ideal Body Weight
IDECG	International Dietary Energy Consultancy Group
IDL	Intermediate Density Lipoprotein
IGF-1	Insulin-like Growth Factor-1
ITM	Immunoturbidometric
iv	Intravenous
KA	Keto-analogues of essential amino acids
LCAT	Lecithin Cholesterol Acyl Transferase
LDL	Low Density Lipoprotein
LPL	Lipoprotein Lipase
LRNI	Lower Reference Nutrient Intake
LSD	Least Significant Difference
LVH	Left Ventricular Hypertrophy
MAMC	Mid Arm Muscle Circumference
MCH	Mean Corpuscular Haemoglobin
MCV	Mean Corpuscular Volume
MDRD	Modification of Diet in Renal Disease study
MUAC	Mid Upper Arm Circumference
NAPRTCS	North American Pediatric Renal Transplant Co-operative Study
NAS	No Added Salt
NB	Nitrogen Balance
NI	Nitrogen Intake
NIR	Near Infra-red
NKF-DOQI	National Kidney Foundation - Dialysis Outcomes Quality Initiative
NUN	Non-urea Nitrogen
OTC	Over The Counter
PABA	P-Amino Benzoic Acid
PAL	Physical Activity Level

Abbreviation	Full Term
PEM	Protein Energy Malnutrition
PNA	Protein Nitrogen Appearance
PTH	Parathyroid Hormone
QC	Quality Control
RBP	Retinol Binding Protein
RDA	Recommended Dietary Allowance
REIN	Ramipril Efficacy In Nephropathy study
rhGH	Recombinant Human Growth Hormone
rhuEPO	Recombinant Human Erythropoietin
RNI	Reference Nutrient Intake
ROC	Receiver Operating Characteristic
RRT	Renal Replacement Therapy
RVT	Renal Vein Thrombosis
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDS	Standard Deviation Score
SGA	Subjective Global Assessment
TEE	Total Energy Expenditure
TG	Triglyceride
TIBC	Total Iron Binding Capacity
TNA	Total Nitrogen Appearance
TSAT	Transferrin Saturation
TSF	Triceps Skinfold
UN	Urinary Nitrogen
UNA	Urinary Nitrogen Appearance
UNIANOVA	Univariate Analysis Of Variance
UUN	Urinary Urea Nitrogen
VLDL	Very Low Density Lipoprotein
WHO	World Health Organisation

Chapter One

INTRODUCTION

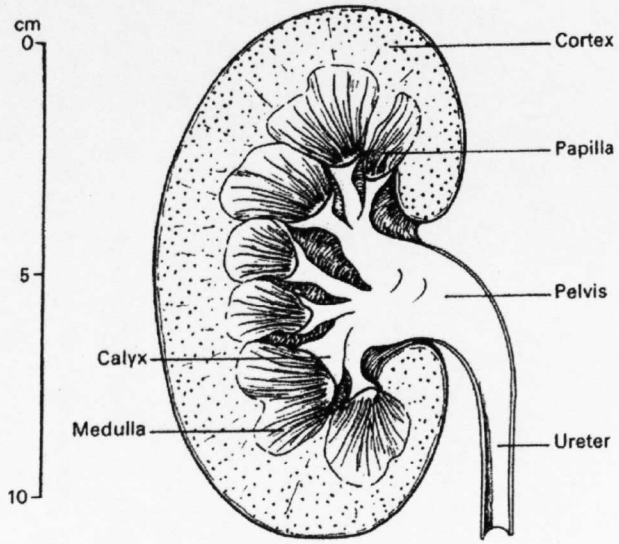
1.1 Role of the Kidney

Metabolism of nutrients results in the production of waste by body cells, including carbon dioxide and excess water. Protein catabolism produces toxic nitrogenous wastes such as ammonia and urea. In addition, many of the essential ions such as sodium, chloride, potassium, sulphate, phosphate and hydrogen tend to accumulate in excess of the body's needs. All the toxic materials and the excess essential materials must be eliminated. The kidneys are responsible for regulating the composition and volume of blood and for removing wastes from the blood in the form of urine. Urine is excreted from each kidney through its ureter and is stored in the urinary bladder until it is expelled.

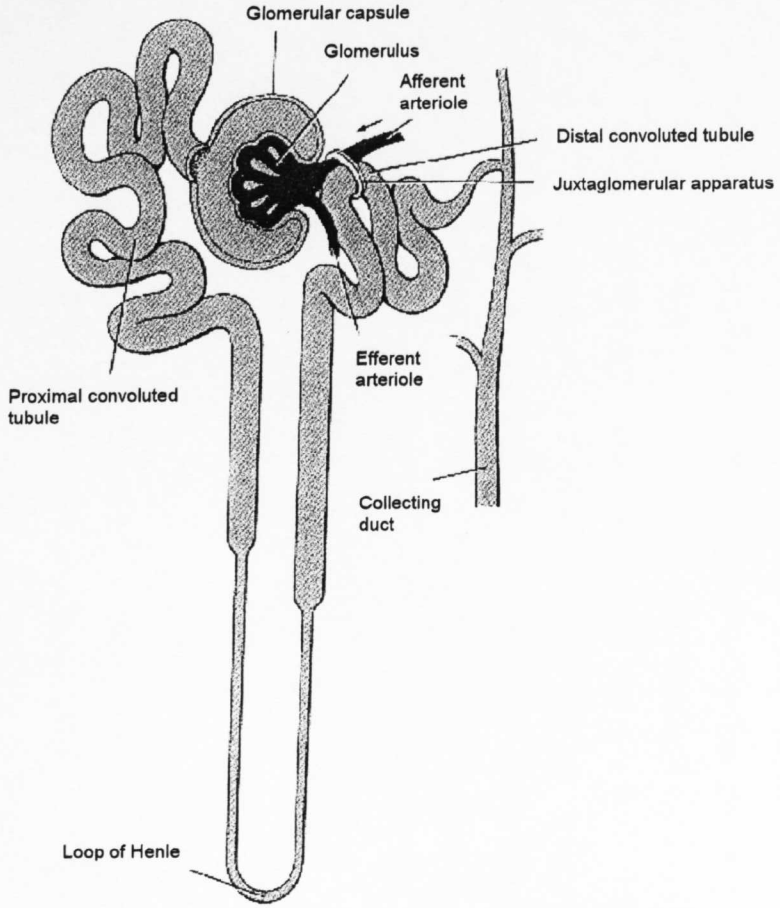
The kidney consists of an outer cortex and an inner medulla, which together form the parenchyma (Figure 1.1 a). The parenchyma of each kidney consists of approximately 1 million microscopic units called nephrons, which are the functional units of the kidney (Figure 1.1 b). Nephrons carry out three important functions. They control blood concentrations and volume by removing selected amounts of water and solutes, help to regulate blood pH, and remove toxic wastes from the blood. The nephron begins as a double-walled cup, called the glomerular (Bowman's) capsule in the cortex of the kidney, which surrounds a capillary network known as the glomerulus, and together is referred to as the renal corpuscle. The hydrostatic pressure within the glomerular capillaries results in the filtration of fluid into the Bowman's capsule. The visceral layer of the glomerular capsule and the endothelium of the glomerulus form an endothelial capsular membrane, which is responsible for the filtering of water and solutes in the blood. Large molecules, such as proteins do not normally pass through it. The filtrate, formed at the glomerulus, passes into the proximal renal tubule which

Figure 1.1 Diagrammatic representations of the kidney

a) Cross-section of an adult kidney (adapted from Cameron, 1981)



b) Nephron (adapted from Tortora & Anagnostakos, 1984)



contain microvilli for increasing reabsorption and secretion, through the loop of Henle, to the distal convoluted tubule, which connects with a collecting duct, taking the formed urine to the renal pelvis for elimination. The filtrate is modified according to the needs of the body by the selective reabsorption of its constituents and of water. The amount of filtrate that flows out of all the renal corpuscles of both kidneys every minute is known as the glomerular filtration rate (GFR). In a normal adult, this rate is about 120 ml/min, equivalent to 180 litres per 24 hrs, of which 99% is reabsorbed back into the blood such that only 1-1.5 ml/min is excreted, equivalent to approximately 1-2 litres per day. Measurement of glomerular filtration rate is used to determine the level of kidney function in clinical practice, for both screening purposes and to determine the degree of progression of disease over time.

The kidneys are also the exclusive site for production of 1,25-dihyroxy vitamin D, the most active metabolite of the vitamin, which acts on the intestine to increase calcium absorption and maintains normal mineralisation of bone. The kidneys also produce erythropoietin and renin. Erythropoietin is a hormone that acts on the bone marrow to increase production of red blood cells. Renin is released from the kidneys in response to a low blood pressure or sodium deficiency. Renin enhances the production of angiotensin, which increases blood pressure directly and also stimulates the production of aldosterone, a hormone responsible for the control of renal tubular reabsorption of electrolytes.

1.2 Chronic Renal Insufficiency

Loss of renal function, otherwise referred to as chronic renal insufficiency (CRI), is an uncommon problem in paediatrics, but early recognition is important for maximising growth and minimising complications. Patients with progressive renal insufficiency need careful follow-up in an attempt to slow progression where possible, to prevent complications and to prepare the children and their families for appropriate renal replacement therapy (RRT). This management requires specialist expertise, with consideration of psychosocial and nutritional needs in addition to medical and nursing requirements, and hence treatment is suggested to be best aggregated in a few specialist centres able to provide this range of support (BAPN, 1995). Providing adequate nutrition for a child with end stage renal disease (ESRD) has been reported by parents to

be one of the most stressful factors that they have to face in the total provision of care for their child (Norman et al, 1995).

The incidence of CRI in children is not known but the number of children on ESRD treatment programmes has risen from 6.6 per million of the child population (aged <15 years) in 1984 to 9.7 in 1992 (Renal Association, 1997). The Paediatric Renal Registry (UK Renal Registry Report, 2000) states that the prevalence is now 12.2 per million total population, with an incidence rate of 1.7 per million total population per year. The increase is principally due to the treatment of infants who have a prolonged duration of care, compared with older patients.

The diseases associated with CRI in children have been described by Foreman & Chan (1988), with congenital malformations (obstructive uropathy, hypoplasia/dysplasia and reflux nephropathy) accounting for the largest percentage of renal failure (52%), followed by glomerulonephropathies (33%), and vascular disorders such as haemolytic uraemic syndrome (HUS) and renal vein thrombosis (RVT) accounting for just 5%. The North American Pediatric Renal Transplant Co-operative Study (NAPRTCS) annual report of CRI (Fivush et al, 1998) describes similar findings, as illustrated in table 1.2, with nearly two thirds of children exhibiting a structural anomaly. In patients with congenital abnormalities, as observed by Wingen and colleagues (1997), the mean decrease in GFR per year tends to be low, of the order of 2.5 ml/min/1.73m^2. Those children with glomerulonephropathies however, showed a greater rate of progression of CRI, with a reduction in GFR of 4.7 ml/min/1.73m^2 per year.

Table 1.2 Summary of primary causes of CRI in children (Fivush et al, 1998)

Primary diagnosis (% children)	< 2 years	2-6 years	6-12 years	12-20 years
Obstructive uropathy	27	32	27	20
A/hypo/dys/ plastic kidney	36	24	17	11
Reflux nephropathy	4	6	12	11
Glomerulonephritis	1	5	8	19
Haemolytic uraemic syndrome	1	4	2	2

The progression of CRI can be divided into 4 stages (Hanna et al, 1991):

- Stage 1 (**mild**) GFR 50-75% normal. Few clinical or biochemical abnormalities are evident when the GFR is above 60% of normal (75 ml/min/1.73m^2) (Hellerstein et al, 1987).

- Stage 2 (**moderate**) GFR 25-50% normal. Blood urea and creatinine concentrations start to increase in an exponential manner. Mild anaemia, nocturia and an increase in parathyroid hormone (PTH) are noted. Renal regulation of water and electrolyte balance becomes limited, which may be accompanied by acidosis.

- Stage 3 (**severe** - chronic renal failure (CRF)) - GFR 10-25% normal. Marked anaemia, acidosis, hypocalcaemia, hyperphosphataemia and renal osteodystrophy are often seen. Anorexia, growth retardation and uraemia may occur.

- Stage 4 (**ESRD**) GFR <10% normal. Patients are prepared for a dialysis and transplantation programme. Children receive RRT once they exhibit signs of lethargy, being unable to attend school, loss of growth velocity, emesis and other signs of uraemic toxicity, oliguria or untoward deterioration of biochemical markers.

Identification of GFR is important. The first aim of the study was to assess the validity of the current method of estimation of GFR (from a creatinine/ height formula) in comparison to a proposed alternative based on serum cystatin C, in the presence of a gold standard, as a screening tool for mild CRI. In addition, this appears to be the first study to obtain serial measurements of cystatin C alongside creatinine/ height for measuring the progression of CRI, although unfortunately serial ^{51}Cr-EDTA measurement were not available for comparison, thereby limiting the conclusions that can be made from this data. It has however, been reported due to the absence of any other longitudinal data on cystatin C in the literature at the current time, with the aim of highlighting areas that require further research. As this aim concerns evaluation of methodology, which is separate to the issues concerning the effects of dietary management on nutrition, growth and blood biochemistry outcomes, it is dealt with in isolation, in a chapter dedicated to estimation of GFR (chapter 4). The classification of children by GFR and estimation of subsequent progression of CRI during the study will be referred to when describing clinical outcomes.

Therapeutic approaches to CRI

A number of therapeutic approaches have been investigated in order to attenuate the build up of waste products which may lead to metabolic changes such as acidosis, hyperlipidaemia, hyperkalaemia and renal osteodystrophy in patients with progressive renal failure (Curtis, 1990; Bourgoignie, 1992). The prevalence of ESRD is increasing world-wide and the provision of adequate treatment to all is absorbing a large proportion of the health-care budget (Ruggenenti et al, 2001). Since rationing of dialysis or selecting out certain patients from receiving treatment is not ethically possible, attempts should be made to prevent the progression to ESRD. The notion of renoprotection is developing into a combined approach to renal diseases, the main measures being pharmacological control of blood pressure and reduction of proteinuria (Ruggenenti et al, 2001). Conservative management of CRI therefore, is aimed at (Yang et al, 1988-89):

- Detecting reversible and treatable factors responsible for the condition
- Obtaining maximal benefit from nutritional and metabolic therapies
- Minimising and if possible preventing extrarenal and iatrogenic complications
- Optimising transition to renal replacement therapy (dialysis or transplantation)

A nutrient is currently defined as a substance that either serves as a fuel for metabolism, as a component for tissue accretion or maintenance, or a substance that regulates cellular and metabolic processes (Sedman et al, 1996). Six classes of nutrients exist; water, carbohydrates, fats, proteins, vitamins and minerals. In recent years, the goal of nutritional therapy for children with CRI has focused on dietary modifications that aim to treat symptoms resulting from defective renal clearance of waste products, preserve native renal function, maintain/improve nutritional status and promote growth and maturation (Hanna et al, 1991).

Nutritional requirements in CRI

Foreman and colleagues (1996) for the North American multicentre Growth Failure in children with Renal Diseases (GFRD) study identified the need to establish nutritional recommendations for children with CRI. Their subsequent recommendations however, were concerned with individual nutrients and not how they could be achieved in practice (Sedman et al, 1996). They also therefore did not address how altering the intake of foods has a knock on effect on the intake of other nutrients, and subsequent

need for medications. Wingen et al (1997) on behalf of the European study group involved in observing the effects of a protein restricted diet on the progression of CRI in children, reported an adequate level of adherence to the diet. Whether this level of dietary counselling could be maintained in a clinical setting however, remains doubtful. This study was therefore designed to address some of these issues, via observing the impact that a current joint medical and dietetic package of care has on the progress of children with CRI over a 2 year period in an established paediatric renal unit (aims 2-4).

Aim 2 was to observe any differences that may exist between children with 'normal' renal function, and those with mild, moderate and severe CRI from a cross-sectional comparison of nutrition, growth and blood biochemistry. Subsequently, the three groups of children with CRI were followed for a period of two years and received a joint package of medical and dietetic care during this time. Aim 3 was therefore to assess the progress of these children in relation to nutrition, growth and blood biochemistry variables, for the cohort as a whole and for the individual groups of CRI over the two year period. The fourth and final aim was to determine whether there were aspects of the dietary advice provided which were more easily adhered to than others, so that future advice and recommended targets could be more realistically achieved, thereby promoting concordance to treatment.

A broad literature review is therefore required, as the current dietetic 'package of care' for children with CRI is multi-factorial. The following sections of this chapter are dedicated to currently debated issues, which surround present joint dietetic and medical management. Attempts are made in the study unit to ensure that children obtain optimal nutrition for growth, through provision of adequate energy (whilst avoiding exacerbation of hyperlipidaemia), control of osteodystrophy and prevention of iron deficiency anaemia, and it is hoped that the study will be able to support the importance of these measures. Benefits from the control of hypertension, proteinuria and avoidance of excessive intakes of protein, phosphate and salt are not so well-established in the unit for limitation of progression of renal failure, and these issues will be explored.

The rationale behind the development and design of this study are detailed in the last section of this chapter, following identification of available literature concerning a majority of the current issues involved in the dietetic management of children with

varying degrees of severity of CRI. The studies described are frequently concerned with adults, due to a lack of studies pertaining to the same issues in children. This is partly associated with the smaller numbers of children available, where large-scale studies would require collaborative work between centres. Extrapolation of findings in adults to children should be treated with caution however, and in some circumstances are not possible. For example, direct comparisons of blood pressure are not possible, as body size acts as an independent factor, with blood pressure increasing with size. Goals for blood pressure treatment in adults to prevent progression of renal function are therefore likely to be higher than for children. In addition, a number of the larger studies concerning the relationship between sodium intake and hypertension were not only conducted in adults rather than children, but also in adults without renal insufficiency. It may be that variations in sodium intake have a different effect on blood pressure in adults and children with CRI compared to that in people without renal failure. To further complicate matters, some people with moderate to severe CRI exhibit polyuria, whereby they lose salt in the urine, and in these instances, recommendations for reducing salt intake to 80-100 mmol/d may not be appropriate. The recommendations made for joint medical and dietetic practice for children with CRI in the following chapters are thus based on best available current evidence and/ or practice, which unfortunately may only have been derived from adult data. By providing an overview of the current literature, many areas are highlighted where further research is necessary, particularly in relation to children, where it is important to establish, whether it is appropriate that recommendations made for adults can equally be applied to children.

1.3 Literature Review

1.3.1 Progression of CRI and blood pressure

A strong and independent, graded association between both systolic and diastolic blood pressure and ESRD was identified by the Multiple Risk Factor Intervention Trial (MRFIT, 1982). Perry and colleagues (1995) found a similar log-linear relationship between baseline blood pressure and risk of ESRD, with a pre-treatment diastolic blood pressure (DBP) > 118 mm Hg being associated with a fourfold increased risk, compared to a DBP of 90-94 mm Hg. They also found a sixfold increased risk of ESRD for pre-treatment systolic blood pressure (SBP) > 180 mm Hg, compared with men who had a SBP of 131-140 mm Hg. Those men whose SBP fell by more than 20 mm Hg after treatment decreased their risk of ESRD by one third.

The most controversial issue remains as to whether hypertension is the cause or consequence of renal damage (Burbury, 1998). The kidneys exhibit an auto-regulatory phenomenon, whereby when exposed to raised arterial pressure, flow through the renal vasculature is reduced by balanced vasoconstriction of the afferent and efferent arterioles. If nephrons are lost, those remaining are subjected to a compensatory increase in perfusion pressure, resulting in an increased GFR, as is also suggested to occur in association with a high protein intake. Hyperfiltration accelerates glomerular damage and further nephron loss. This mechanism supports the concept of a dynamic feedback loop of exposure to changes in blood pressure and progressive renal damage over time, rather than a cause and effect scenario (Burbury, 1998). Some studies in relatives of patients with essential hypertension have suggested that there may be an underlying impairment of the kidney's ability to excrete sodium (de Wardener, 1990), resulting in 'salt sensitive' individuals.

The Modification of Diet in Renal Disease (MDRD) study found that in patients with CRI, after 2 years follow-up, a 5 mm Hg reduction in mean blood pressure was associated with a 15% reduction in the rate of decline of GFR (Peterson et al, 1995). Locatelli and Del Vecchio (1999) analysed the effect of the 2 different blood pressure target levels to which patients in the MDRD study were assigned, and demonstrated that strict blood pressure control for a mean projected period of 9.4 years delays reaching ESRD by nearly 1.2 years. Strict adherence to a low protein diet (0.6 g/kg/d) in patients with moderate CRI for a similar period of time, could delay the beginning of RRT by no

more than one year. Strict blood pressure control is therefore a marginally more effective and less demanding treatment than low protein diets which place the patient at risk of malnutrition, in delaying the progression of CRI. Analysis of the combined effects of a low protein diet and strict blood pressure control over 10 years of projected follow up, suggests that they are synergistic and could delay reaching ESRD by nearly 2.5 years (Locatelli & Del Vecchio, 1999).

1.3.2 Hypertension and dietary intake

Sodium balance is usually maintained by appropriate alterations in urinary sodium excretion when sodium intake changes. Reductions in GFR tend to be associated with decreased tolerance to variation in dietary intake of sodium. Infants and young children with renal damage secondary to obstruction present with tubular dysfunction, resulting in excessive excretion of sodium, and thus require salt supplementation to prevent volume contraction and to improve growth. Most children with chronic glomerulonephritis are only able to tolerate a limited intake of sodium without aggravating hypertension and oedema. Hypertension is commonly associated with CRI but it is yet to be determined whether lowering blood pressure (BP) in high risk individuals, before evidence of renal dysfunction occurs, reduces the rate of progression (Burbury, 1998).

The British Hypertension Society guidelines for hypertension management, state that non-pharmacological measures should be utilised in all hypertensive and borderline hypertensive people (Ramsay et al, 1999). Optimal blood pressure treatment targets should be, using antihypertensives where indicated, a systolic BP < 140 mmHg and diastolic BP < 85 mmHg, with a minimum acceptable level of control of <150/< 90 mm Hg. Blood pressure increases throughout childhood and the goals of therapy for children with CRI, as stated by the Renal Association (1997), should be to maintain BP within 2 standard deviations (SD) (below the 95th percentile) of the mean for normal children of the same height and sex (de Man et al, 1991). There is considerable evidence to support an interaction between genetic and environmental factors in determining blood pressure and occurrence of hypertension, and the idea has developed that essential hypertension is a process that starts early in life (WHO study group, 1985). Non-pharmacological therapy involving weight reduction, exercise and dietary intervention (sodium and potassium) should be commenced in children with high

normal blood pressure (90-95th percentile) and to complement those treated for severe hypertension (Sinaiko, 1994).

The international epidemiological study of adults, INTERSALT (1988), reported a weak but significant association of dietary salt with blood pressure, stating that 'sodium was significantly related to the slope of blood pressure with age, but not to median blood pressure or prevalence of hypertension.' The populations selected ranged from a Brazilian tribe (the Tanamamo) with a mean daily salt intake of 12 mg, to Northern Chinese factory workers with a mean intake of 14g. The differences in diet, climate, culture and lifestyle that might influence blood pressure were extreme and thus likely to contribute to inconclusive results. Body size was reported to be the major determinant for blood pressure variability, and both systolic and diastolic blood pressure decreased in response to weight loss (Dyer et al, 1989). Following further analysis of the INTERSALT data however, the association between sodium excretion and blood pressure was found to be stronger when body mass index (BMI) was not adjusted for (Elliott et al, 1996). Thelle (1996) suggests that BMI was likely to have emerged as the strongest variable in a multiple regression analysis, as BMI correlates with sodium excretion and is measured more accurately than sodium excretion.

The updated INTERSALT analysis suggests that salt intake (as measured by sodium excretion) is the most significant factor in the development of hypertension (Elliott et al, 1996). As salt intake rises, there is an associated and significant rise in blood pressure and the size of this effect appears to increase with age. A study on chimpanzees showed that after adding 100 mmol of sodium per day to their food for 19 weeks, their systolic blood pressure increased by 12 mm Hg (Denton et al, 1995). Blood pressure rose further with further increases in sodium intake and fell when sodium supplementation was stopped. Midgley et al (1996) however, conducted a large meta-analysis on 56 published randomised controlled trials, including a number of trials involving normotensive persons and concluded that a salt reduction of 100 mmol/d reduced blood pressure by 3.7/0.9 mmHg in hypertensive patients and only by 1.0/0.1 mmHg in normotensive individuals. This analysis however may have incorporated bias, in that the normotensive patients tended to be younger than their hypertensive counterparts. A recent review of diet and blood pressure in children and adolescents suggests that high sodium intakes are related to higher blood pressure (Simons-Morton & Obarzanek,

1997). Sinaiko et al (1993) restricted sodium intakes to 1,600mg (70 mEq)/day for a period of 3 years in a group of adolescents. They found difficulty in achieving this reduction however, particularly in adolescent males, despite intensive dietary reinforcement and subsequently were unable to demonstrate a benefit upon blood pressure. The females who were able to maintain a low-sodium diet over the 3-year period however, exhibited a significantly decreased rate of rise in blood pressure.

Patients treated at the haemodialysis centre in Tassin, France are repeatedly reported to have the best survival and lowest mortality on maintenance haemodialysis in the world (Charra et al, 1992). Blood pressure control is achieved without drugs in 98.4% of patients on haemodialysis, with mean arterial pressures below 99 mmHg, via means of long haemodialysis sessions, a relatively low sodium dialysate (138 mmol/l) and dietary salt restriction (4-5g/d). Krautzig et al (1998) state that blood pressure control can be achieved without the need for long hours of dialysis, with a moderate salt restriction [< 6g/d (< 100 mmol sodium/d)] and cautious lowering of the dialysate sodium concentration from 140 to 135 mmol/l by 1 mmol/l every 3-4 weeks. This should facilitate a reduction in antihypertensive therapy. In some patients, lowering the salt load restored taste acuity for salt, which may have facilitated dietary compliance. In addition to the relationship described between a high salt intake, hypertension and progression of renal disease, a high salt intake has also been linked to the development of left ventricular hypertrophy, stroke, asthma, cancer of the stomach and bone demineralisation (osteoporosis) (Antonios & MacGregor, 1996).

It has been advocated that a modified sodium intake of 80-100 mmol/d, equivalent to approximately 5-6g salt per day (1g sodium ≡ 2.5 g salt), regarded as a 'No Added Salt' (NAS) diet, should form part of the healthy eating diet for the whole population to prevent hypertension (Law, 1991; WHO, 1999), with the exception of those patients who are salt losers and those on certain medications (McCarron, 1995). High sodium intakes early in life may condition children to a lifelong high salt appetite (Lauer et al, 1978). Discretionary salt (that added in cooking and at the table) is reported to account for about 15% of total sodium intake, whilst approximately 75% is derived from salt that is added during the processing of manufactured foods (Elliott et al, 1996). Foods such as bread, tinned products and processed meats are particularly and probably unnecessarily high in salt. Salt is used heavily in industry due to it being a cheap,

readily available flavour enhancer and it facilitates water retention in products, thereby increasing the weight of the product for no extra cost (some meat products can have their weight increased by 20-30%). Soft drink manufacturers also entertain a commercial interest in high salt intakes, as a 30% reduction in salt intake would result in a decline in soft drink sales (MacGregor, 1998). The major sodium sources identified in young children, were derived from convenience foods such as beefburgers, baked beans and soups, offered as substitutes for the typical refusal of family meals by pre-school children (Allison & Walker, 1986). MacGregor et al (1986) found that children aged between 4-6 years of age had sodium excretion levels that were 1.5 times higher than in adults and 3.5 times higher if expressed in relation to creatinine excretion.

A Consensus Action on Salt and Hypertension (CASH) group has been established with the remit of 'working with' the food industry to reach a consensus on salt and blood pressure and then to devise a means to reduce the amount of salt in food (MacGregor & Sever, 1996). The government has pledged in a recent White Paper to work with the food industry to reduce the amount of salt in processed food by 30% over the next 5 years (DoH, 1999). As MacGregor (1998) states, simply comparing the salt content of a food to the concentration of Atlantic seawater (1g sodium/ 100g), should help people decide whether they wish to eat the equivalent of seawater or not! Sodium chloride increases blood pressure due to its effect on extracellular fluid volume and renal excretion of salt, whereas other salts have little effect (Weinberger, 1987). As a result, some manufacturers have part substituted potassium for the sodium salt, which may be of benefit for the general population but poses a greater problem for those children and adults with severe CRI, where potassium restriction is often necessary. In addition, alternative salts do not address the need to wean consumers away from a liking for salt.

The INTERSALT study (1988) found a strong inverse relationship between urinary potassium excretion and blood pressure. Whelton et al (1997) conducted a meta-analysis of trials observing the effects of oral potassium on blood pressure in adults, and concluded that a low potassium intake may play a role in the development of hypertension. They recommend increasing potassium intake for prevention and treatment of hypertension, especially in people unable to reduce their sodium intake. Sinaiko (1993) noted in adolescents that the rate of rise of blood pressure over a 3 year period was significantly reduced in girls receiving potassium supplementation, but

appeared to be of little benefit in boys. Potassium is primarily found in fruits and vegetables and relatively large amounts are required to have an impact on blood pressure. Unfortunately, potassium-rich foods tend to be contraindicated in children with a GFR < 25ml/min/1.73m^2 in order to maintain serum potassium levels within the normal range. Unlike the review in adults (Whelton et al, 1997), the relationship between potassium and blood pressure in children, as outlined in a review by Simons-Morton & Obarzanek (1997) appeared to produce less conclusive results as to the benefits of increasing potassium intake on blood pressure.

An updated meta-analysis of studies concerning the relationship between calcium intake and blood pressure concludes that an increased calcium intake is associated with a modest reduction in SBP and DBP in adults (Griffith, 1999). The Dietary Approaches to Stop Hypertension (DASH) multicentre, randomised controlled trial was designed to investigate the effect of the entire diet on blood pressure rather than individual nutrients. It is the first study to demonstrate that a combined alteration in diet i.e. a diet rich in low fat dairy products, fruit and vegetables can produce reductions in blood pressure of a similar magnitude to those produced by anti-hypertensive medications, compared with the control diet (Appel et al, 1997). The most recent DASH trial studied the additional effects of sodium intake on the original DASH diet (Sacks et al, 2001). Participants consumed foods with high (150 mmol/d ≡ 9g salt), intermediate (100 mmol/d ≡ 6g salt) or low sodium (50 mmol/d ≡ 3g salt) levels for 30 consecutive days each in random order. Systolic and diastolic blood pressures were consistently lower for the DASH diet group compared to controls, at each of the 3 levels of sodium intake. The level of dietary sodium had twice as great an effect on blood pressure with the control diet as it did with the DASH diet. As compared with the high sodium control diet, the low sodium DASH diet reduced mean systolic blood pressure in normotensives and hypertensives by 7.1 mmHg and 11.5 mmHg respectively. Renal diets, which tend to involve restriction of dairy products and certain fruits and vegetables are unfortunately incompatible with emerging recommendations derived from the DASH study (Ramsay et al, 1999). It has not yet been demonstrated however, whether hypertensive renal patients would respond to the diet in the same way.

The North American multicentre Growth Failure in Children with Renal Disease (GFRD) study observed the relationship between calcium, phosphorus and sodium

intake with blood pressure in children with CRI, and found that blood pressure levels were not related to sodium intake or GFR (Trachtman et al, 1995). Both SBP and DBP were found to be inversely related to mean calcium and directly related to mean phosphorus intakes in black children, whereas only a correlation between DBP and mean phosphorus intake was demonstrated in white children, suggesting racial differences. Mean calcium intakes were sub-optimal for both racial groups, with white and black children achieving 81% and 74% of the recommended dietary allowance (RDA) respectively, whereas phosphorus intakes were adequate for both. There was a direct relationship between both SBP and DBP and serum PTH concentration in the entire study group. Hyperparathyroidism induces hypertension by increasing ionised calcium levels, decreasing GFR and causing tubular damage. Trachtman et al (1995) suggest that in addition to the importance of dietary calcium supplementation in the prevention of hypocalcaemia, hyperphosphataemia and renal osteodystrophy in children with CRI, an adequate intake of calcium may contribute to the maintenance of normal blood pressure alongside avoidance of excessive dietary phosphorus.

Levey et al (1995) compared the blood pressure responses of men consuming low sodium diets differing in dietary calcium for two 6 week periods. Unexpectedly, a significant decrease in DBP was observed in the low calcium group during the 6 weeks of strict dietary supervision. The high calcium group showed no significant changes in either DBP or SBP. Previous dietary intakes were examined to determine whether blood pressure responses to the strictly supervised diet could be predicted. A significant correlation between the change in ratio of sodium to calcium was noted, with a larger ratio of sodium to calcium in the typical diet resulting in a larger decrease in blood pressure during the supervised diet. The large reduction in sodium in the low calcium group may have been responsible for the unexpected reduction of blood pressure in this group, and suggests that change in sodium intake may be more important than calcium intake. It is difficult to adhere to a low sodium diet (Sinaiko et al, 1993). As the magnitude of dietary change may be more important in reducing blood pressure than attempting to achieve a target figure, it may be more effective to focus on specific changes to the individual's diet than to set target levels for the general population (Levey et al, 1995). Levey and colleagues (1995) suggest decreasing an individual's sodium intake by 1,000 mg/d and increasing their calcium intake by 400 mg/d, an

approach that may improve dietary compliance, thereby increasing the chance of a positive blood pressure response.

Attempts to reduce sodium intake from poor nutritional sources such as soups, sauces and salty snacks would seem appropriate advice for children with CRI who exhibit no evidence of tubular dysfunction. Until the manufacturers manage to reduce the salt content in a wide variety of processed foods, little more can be readily achieved without the use of unpalatable low salt products. Children with mild CRI are unlikely to have polyuria and can safely be prescribed a salt restricted diet as illustrated in the appendix. This approach may potentially help to reduce the rate of progression of their disease, if it contributes to normalising their blood pressure. Infants and children with more severe renal failure however, are more likely to have a higher requirement for sodium, and in some cases require a salt supplement. These children are usually relatively easy to identify from their large reported fluid intake. They are often found to also have a liking for savoury foods. It is not appropriate for children requiring salt supplements or exhibiting polyuria to be placed on a salt restricted diet. As their renal function continues to deteriorate however, they lose their ability to excrete fluid, and then salt restriction becomes imperative as a means of minimising fluid retention. As a result, the severe group will be heterogeneous in relation to their targets for sodium intake.

1.3.3 Progression of CRI and proteinuria

Significant baseline proteinuria tended to predict a greater rate of progression in the MDRD study, compared to those without proteinuria (Peterson et al, 1995). Percentage reduction in proteinuria and reduction in mean decline in GFR was greatest in those patients who achieved the lowest blood pressure goal. Bertani & Remuzzi (1990) found that altered glomerular permeability to macromolecules and resulting plasma proteins leaking across the damaged glomerular membrane and undergoing reabsorption in the tubule, initiated a nephrotoxic inflammatory cascade. Plasma proteins ultrafiltered in excess have been shown to be directly toxic to tubular epithelial cells, inducing production of proinflammatory cytokines and extracellular matrix proteins, which in turn promote interstitial fibrosis (Abbate et al, 1998). Remuzzi showed that "mending the holes" in the glomeruli by means of an angiotensin-converting enzyme inhibitor [ACEI (Ramipril)] could halt disease progression, irrespective of dietary protein intake (GISEN Group, 1997).

ACE inhibitors reduce intraglomerular capillary pressure and subsequently albumin excretion, and inhibit the conversion of angiotensin I to angiotensin II, thereby limiting activation of tubular epithelial cells (Maschio et al, 1996). Results from the ACE inhibition in progressive renal insufficiency (AIPRI) trial using the ACEI benazepril, produced a 53% risk reduction in reaching RRT or doubling of serum creatinine in patients with mild or moderate CRI (Maschio et al, 1999). The risk reduction was greater in those with mild CRI or with proteinuria greater than 3g per 24 hours at baseline. There was a large difference in blood pressure control between the ACEI and placebo group however, making it impossible to separate the beneficial effects of blood pressure control from any other effect specific to the ACEI. ACE inhibitors nevertheless, have been shown to have a renoprotective effect independent of blood pressure control alone (Kamper et al, 1992). The Ramipril Efficacy in Nephropathy (REIN) study exhibited comparable blood pressure control between the ACEI and conventional treatment group, and a 74% reduction in the number of women (40% of men) reaching ESRD in those receiving an ACEI was observed (Ruggenenti et al, 1998a). A target BP of 125/75 mmHg, equivalent to a mean arterial pressure of $\leq$92 mmHg [calculated as (systolic + 2 diastolic)/3] has since been recommended by the MDRD study group for patients with urinary protein excretion >1 g/d, with an ACEI being encouraged as the agent of first choice (Lazarus et al, 1997). To achieve such rigorous blood pressure control, two or three different antihypertensive agents will frequently be required in addition to lifestyle modification (Bakris, 2000). Dietary salt restriction significantly enhances the efficacy of ACE inhibitors in diminishing proteinuria (Heeg et al, 1989). Salt restriction has been found to be effective in attenuating the progression of renal damage independently from its antihypertensive effects, and those patients ingesting a high sodium intake showed a marked worsening of proteinuria (Cianciaruso et al, 1998). The authors however, were unable to distinguish whether this was in part due to a coincidental parallel lower protein intake and further studies are required to assess the importance of dietary sodium intake in the progression of CRI.

1.3.4 Progression of CRI and protein and/ or phosphate restricted diets

The discovery that changes in blood urea levels correlated with dietary protein modification in normal individuals, demonstrated that short term beneficial effects could potentially be obtained from a low protein diet in patients with renal failure (Addis et al, 1947). Further interest in dietary therapy developed when a severely protein-restricted diet was advocated for symptomatic relief of the uraemia of end-stage renal disease; a condition associated with raised plasma urea levels, nausea, vomiting, pruritis, bone pain, shortness of breath, fatigue, weakness and anorexia (Giovannetti & Maggiore, 1964). There is little evidence however, that uraemia per se directly contributes to these symptoms, and it may be that metabolites of protein catabolism other than urea are toxic (Wilson, 1971), affecting growth either directly or indirectly by causing anorexia. Until the uraemic toxin is elucidated, plasma urea continues to be used as a marker of uraemic symptoms, despite there being a poor correlation between the two.

More recently there has been much debate and controversy as to whether a reduction in the dietary protein intake of patients with renal damage can protect the remaining nephrons, and thereby delay the progression of CRI (El-Nahas & Coles, 1986). The basis for this hypothesis was derived from experimental animal studies, where acute increases in renal blood flow and glomerular filtration rates following protein ingestion have been suggested, by cumulative effect, to be responsible for sustained hyperfiltration and accompanying renal hypertrophy in animals maintained on high protein diets. In animals with induced renal failure, the increased burden of a high protein intake may induce a pathological process of sclerosis in the glomeruli of residual nephrons (Hostetter et al, 1981; Brenner et al, 1982). When sclerosis obliterates the glomerulus, the remaining nephrons have increased workloads, which perpetuates the cycle of sclerosis and deterioration of renal function. Hostetter and colleagues (1981) have demonstrated that protein restriction (from 24% to 6% of energy) can lower the pressure and flows acting on remnant glomerular capillaries, limiting excessive hyperfiltration and thereby forestalling progressive glomerulosclerosis and subsequent deterioration of renal function. A study in uraemic rats fed differing amounts of protein revealed that those fed less protein survived longer (Kleinknecht et al, 1979) but at 6% protein (i.e. a suboptimal diet for growing rats), growth retardation was observed (Salusky et al, 1981).

Studies on protein restriction in humans have mostly been undertaken in adults and many suffer from methodological shortcomings such as small numbers of patients, heterogeneous population for age and level of CRI, use of plasma creatinine as a measure of GFR (a low protein diet will decrease creatine intake and thus creatinine production), uncontrolled energy intakes and poor dietary compliance (El-Nahas & Coles, 1986). Adherence to a low protein diet often results in a drift upward in protein intake with time for treated groups (Fouque et al, 1992). Several studies in adults suggest that restriction of protein early in the course of renal disease may slow the rate of progression of renal failure (Maschio et al, 1982; Barsotti et al, 1983; Rosman et al, 1984). Rosman and colleagues (1984) prescribed 0.6g protein/ kg/d for those with a GFR between 30-60 ml/min/1.73m^2 and attributed their good dietary compliance to frequent review (3 monthly) by the dietitian. In those with proteinuria (>0.5g/ 24 h), a significant reduction in proteinuria was observed whilst on the low protein diet, which may have an implication in the progression of renal disease, as those renal disorders accompanied by proteinuria tended to have a worse prognosis than those without proteinuria (Klahr et al, 1994; Wingen et al, 1997). The Italian multicentre study (Locatelli et al, 1991) did not show any difference in the rate of progression between the two groups. The difference between the two groups was not large however, with the control group following a typical Italian diet, which is relatively low in protein (1g protein/kg/d), and the reduced protein group (0.6g/kg/d) failing to meet their prescription due to poor compliance.

Klahr et al (1994) for the MDRD study found that a prescribed protein intake of 0.6g/kg/d (actual protein intake approximated 0.7g/kg/d) provided a small benefit in delaying progression from the fourth month onward, in those patients with a GFR between 25-55ml/min/1.73m^2. They noted a more rapid deterioration in renal failure in patients with a higher degree of proteinuria. The overall decline in GFR however, was slower than predicted. A longer study period may have been necessary to show a more significant benefit and most patients had uropathy and congenital nephropathies which tend to exhibit a slow progression towards renal failure. Analysis of an additional 13 month period following completion of the study revealed that dietary protein restriction led to a statistically significant protection in patients with more advanced CRI (Levey et al, 1996). Dietary protein restriction (low protein, 0.6 g/ kg/ d or very low protein, 0.3 g/ kg/ d + 0.3 g/ kg amino/ keto acid supplement) was noted to slow the rate of rise of

urinary protein excretion during follow-up. For each reduction in total protein intake of 0.2g/ kg/ ideal body weight (IBW), the mean decline in GFR was reduced by 1.15 ml/min/year (29%). This would translate into a prolongation of time to ESRD by 41%. The results of Levey and colleagues (1996) suggest that a lower protein intake, rather than the keto-acid/ amino acid supplemented diet per se, is associated with a slower progression of renal disease. The trend toward a greater beneficial effect with the very low protein diet compared to the low protein diet, appeared to be associated with improved achievement in meeting the low protein targets. A recent systematic review concluded that reducing protein intake in patients with CRI reduces the occurrence of renal death by about 40%, compared to those on unrestricted protein diets (Fouque et al, 2000).

Those patients expected to respond to a low protein diet tend to be those with a reactive renal vascular bed and mild focal glomerular involvement (El-Nahas et al, 1984), whereby the reduction of hyperfiltration by a low protein diet decreases proteinuria and halts the progression of their renal insufficiency (Aparicio et al, 1989). El-Nahas and colleagues (1984) demonstrated that those with chronic tubular disorders (polycystic kidney disease, tubulointerstitial nephritis) responded well; the best response being in patients with chronic pyelonephritis. A poor response was noted with hypertensive nephrosclerosis. In patients with chronic glomerulonephritis, the response of proteinurea to low protein diets discriminated between those whose renal function did or did not improve. Ruggenenti et al, (1998b) demonstrated that proteinuria is a reliable predictor of the progression of disease in non-diabetic patients with chronic nephropathies.

Protein restriction also reduces phosphate intake which in turn has been reported to reduce the rate of progression (Ibels et al, 1978; Lumlertgul et al, 1986). Maschio et al, (1982) suggested that a restricted protein (0.6g/kg/d) and phosphate (600-750mg/d) diet, supplemented with energy (40kcal/kg/d) and calcium (1,000-1,500mg/d) produced better results in delaying the progression of CRI in patients with only a mild to moderate loss of renal function, compared to those with more advanced renal failure. Phosphate and protein restriction early in the course of renal disease has also been emphasised by Walser (1980) & Barsotti et al, (1983). The benefit of early intervention could be associated with reduced nitrogen load and hyperfiltration of surviving

nephrons, reduced phosphaturia, prevention of secondary hyperparathyroidism, and maintenance of a normal calcium/phosphorus solubility product, thereby decreasing the risk for renal microcalcification (Collier et al, 1978). Walser (1980) believes that a strong case exists for the control of serum calcium and phosphate early in the course of renal failure, in retarding or even halting the progression of CRI. It has been difficult to test the influence of dietary phosphate on progression of CRI due to the fact that phosphate-rich foods are also generally high in protein and that adding phosphorus to a low protein diet can be dangerous, as it can stimulate secondary hyperparathyroidism (Mitch, 1991). Barsotti and colleagues (1984) however, provided low-protein diets (0.6 g/kg) to 55 patients with CRI (mean creatinine clearance of 30 ml/ min) and then varied phosphate intakes (6.5 or 12 mg/kg/d). Patients with a low urinary phosphorus output had no changes or an improvement in creatinine clearance, whilst those with values above 400 mg/d had a decrease in creatinine clearance. Little change in serum phosphate was observed, probably due to the phosphaturic action of parathyroid hormone. The authors conclude that strict dietary phosphate restriction should be prescribed to all patients with early chronic renal failure.

A very low protein diet (0.3-0.4g/kg/d) relieved uraemic symptoms but did not sustain muscle mass or maintain nitrogen balance. Increasing the protein content in the diet to 0.6g/kg/d sustained nitrogen balance in moderately uraemic patients (Kopple & Coburn, 1973), corresponding to the minimum intake recommended by the World Health Organisation (WHO) for healthy subjects (FAO/WHO/UNU, 1985). Nitrogen derived from urea does not appear to contribute substantially to protein nutrition in uraemia. The combination of a very low protein diet (0.3g/kg/d) plus supplementation with essential amino acids (EAA) and/or carbon skeletons (keto-analogs) of essential amino acids (KA), was found to sustain nitrogen balance in patients with a GFR < 5% normal (Mitch et al, 1982). Walser and colleagues (1993) found a ketoacid-amino acid supplement to be more effective in slowing short-term GFR decline than a mixture of essential amino acids. Keto-analogues have been advocated to reduce the accumulation of urea nitrogen, diminish catabolism and thus spare body nitrogen. Such diets have been suggested to delay the need for renal replacement therapy for up to one year (Alvestrand et al, 1983; Mitch et al, 1984), although this issue remains unclear, and it may simply permit the patient to achieve improved concordance with targets, via less stringent restrictions on protein quality (Masud et al, 1994).

The low protein (0.6g/kg) and very low protein diets (0.3g/kg + 0.3g/kg KA mixture) used in the MDRD study (Kopple et al, 1997) were shown to be safe for periods of 2-3 years, although both protein and energy intakes were reduced. Of concern were the small but significant declines in various indices of nutritional status (body weight, percent body fat, arm muscle area, serum transferrin and urine creatinine excretion) which accompanied the reduction in dietary intakes. Percentage body fat was estimated using the equations of Durnin & Wolmersley (1974). To evaluate this further, Kopple and colleagues (2000) correlated GFR with dietary and nutritional parameters and found that protein and energy intakes, serum albumin, transferrin and total cholesterol, and percentage body fat progressively declined as GFR decreased. In general, it was observed that the lower the GFR, the lower were the values for the nutritional parameters. Ikizler and colleagues (1995) stated that caution should be used in prescribing low protein diets, particularly in patients with severe CRI (GFR < 25 ml/min) due to the spontaneous decrease in dietary protein intake and deteriorating nutritional indices observed. Patients with a GFR > 50 ml/min exhibited a mean protein intake of 1g/kg/d which decreased to 0.85g/kg/d in those with a GFR between 25-50 ml/min, 0.7g/kg/d with a GFR between 10-25 ml/min and reached as low as 0.54g/kg/d for patients with a GFR < 10ml/min. They recommend that chronic dialysis therapy should be considered if the patient's dietary protein intake falls below 0.7 g/kg/d despite adequate nutritional counselling. Careful attention should therefore be paid towards energy, vitamin, and mineral intakes, supplementing the diet where appropriate (Blumenkrantz et al, 1980; Kopple et al, 1997; Bircher, 1998), particularly as the nutritional status of patients entering onto the dialysis programme often predicts their subsequent morbidity and mortality on dialysis (Maschio, 1995).

There is some evidence to suggest that progression of CRI is slower on diets based on vegetable (soya) protein than on animal protein. In a group of healthy individuals fed a meat or soya load of equivalent protein content, soya protein was not shown to increase postprandial GFR or renal blood flow, whereas animal protein resulted in an increase in GFR and renal blood flow of approximately 15% (Kontessis et al, 1990). Kontessis and colleagues (1990) suggest that the differences in renal responses to meat or soya derived protein are likely to be associated with the different hormonal responses elicited. Glucagon and renal vasodilatory prostaglandin are two hormones that have been implicated, the latter being associated with both renal haemodynamic changes and

mediation of proteinuria. Secretion of these hormones appears to be blunted after a soya meal. Barsotti and colleagues (1988) have also demonstrated that proteinuria was reduced in patients with diabetic nephropathy who were changed to a diet based on soya protein. Soroka et al (1998) however, conducted a randomised, prospective, crossover trial on 15 adults with GFR's between 15-50 ml/min/1.73m^2 (9 patients completed the study, 2 could not tolerate the soya diet) and found little benefit of soya protein over animal protein based, low protein diets. They were given a diet for a 6-month period on each protein type; 0.75g protein/ kg (soya or animal based) and 32 kcal/ kg body weight. Mean GFR was similar throughout the study and progression slowed equally, by 73% during the 1-year study period as compared with the pre-study period on either diet. Nutritional status was also deemed to be similar between groups, as determined by body mass index (BMI), mid upper arm circumference (MUAC), lean body mass and percent body fat and serum albumin.

A safe and effective therapeutic diet for children with CRI must support growth in addition to delaying the progression of renal insufficiency. Growth rates are slowed by the insufficient provision of protein (Waterlow, 1986). The effect of dietary protein modification in infants with CRI was monitored as part of the feasibility phase of a multicentre controlled clinical trial (Uauy et al, 1994). They observed that a low protein diet (1.4g/kg/d) resulted in slower growth of infants, although there were no significant differences in weight gain or GFR compared to infants on the standard diet (2.4g/kg/d protein). A 3 year prospective study was undertaken by Kist-van Holthe tot Echten et al, (1993) to investigate the effect of a protein restricted diet (0.8-1.1g/kg/d) on renal function and growth in children with CRI (GFR 15-60ml/min/1.73m^2), compared with an ad lib protein intake in controls. No significant difference was observed in GFR between the protein restricted group and controls at the end of the 3 year period. Energy intake was adequate and similar in both groups (>80% of that recommended) and growth was maintained. They conclude that children with CRI do not benefit from moderate protein restricted diets. It may be that a greater protein restriction was necessary to achieve a beneficial effect, but that this should be treated with caution due to the risk of growth retardation.

A large European multicentre, 2 year prospective study was designed to evaluate the effects of a protein restricted (0.8-1.1g/kg), adequate energy diet on the rate of

progression of CRI, growth and development in 191 children, and to evaluate the long-term acceptance of this diet (Wingen et al, 1997). They observed 'no harm, but no benefit either' with this intervention, which again may be a reflection of the caution placed on use of over-restrictive protein diets in children. Care however, should be taken in describing this diet as 'low protein', as the children were reported to be achieving above 125% of the WHO recommended amount for protein (141% on the basis of urinary urea-nitrogen studies), which is greater than the UK reference nutrient intake (RNI) for protein for the normal population (DoH, 1991). Proteinuria (greater than 50 mg protein/kg daily) and hypertension (systolic above 120 mm Hg) seemed to explain a large part of the variability (35%) between the progressive and non-progressive group, and this may be causally related to the decline in GFR.

Jones et al (1983) suggest that a protein-restricted diet supplemented with EAA and KA may be beneficial in children for improving linear growth and nutritional status, as observed from their study in seven prepubertal children with GFR's between 6-13 ml/min/1.73m^2. Both nitrogen and phosphate are reported to be important uraemic toxins, the latter mainly due to its stimulatory effect on the secretion of PTH (Slatopolsky et al, 1972). Jones and colleagues (1983) observed that plasma calcium levels rose in all children despite temporary discontinuation of vitamin D, due to an increase in calcium intake (keto-acids as calcium salts), whilst plasma urea, phosphate and PTH levels fell significantly, associated with reductions in dietary phosphate and protein intakes. Significant increases in mean growth velocity (4.3 to 6.6 cm), growth velocity standard deviation score (SDS) for bone age (-2.07 to 0.44), height SDS for chronological age (-2.92 to -2.63) and upper arm circumference (-0.38 to 0.37) were observed over the 1 year period. The authors suggest that some of the benefits observed may be attributed to improved protein anabolism as reflected by changes in MUAC, serum transferrin and nitrogen balance, and a reduction in hyperparathyroidism. Jureidini et al (1990) demonstrated that a low protein (1-1.2g/kg), low phosphorus (500-1000mg), adequate energy (1-1.2 x RDA for height age) diet combined with EAA and KA (0.3g/kg) was beneficial in delaying the progression of renal failure in 10 children with moderate to severe CRI (GFR 13-48 ml/min/1.73m^2), and was accompanied by an overall improvement in general health.

With increasing uraemia, dietary protein can safely be reduced until protein intake falls close to, but not below the RNI in children, so that growth can be sustained and eating styles can be kept similar to those of healthy children of the same age (Raymond et al, 1990). The diets need to be carefully planned, patients and parents extensively counselled and dietary supplements of energy and micronutrients administered where indicated. Protein should provide 5-10% of total energy intake (Chan, 1973; Hellerstein et al, 1987; Yang et al, 1988-89) and at least 65-70% of protein should be of high biological value (HBV) e.g. milk, eggs, cheese, meat, fish, poultry and pulses, although unfortunately dairy products are also high sources of phosphate and hence have to be restricted (see section 1.3.7). HBV protein minimises urea production by reusing nonessential amino acids for protein maintenance. Ledermann and colleagues (1999) believe that expressing protein as a percentage of energy intake is misleading and protein intake should be expressed per kg body weight. A reduction in the percentage of energy from protein does tend to reflect an increase in energy intake rather than a reduced protein intake. This however, may actually be of more importance than reducing total protein intake in attempting to delay the progression of CRI, through its facilitation of a more positive nitrogen balance and reduction in net urea generation (Kopple et al, 1986). Ledermann et al (1999) concede that plasma urea levels remained low, despite protein intakes exceeding the RNI, as an adequate energy intake was provided.

It appears imperative to elucidate whether a lower protein diet should be recommended for those children with significant proteinuria, in an attempt to reduce proteinuria and hence progression of CRI, as highlighted in adults (Rosman et al, 1984; Klahr et al, 1994; Ruggenenti et al, 2001). In association with the hyperfiltration theory, it has been recommended that reduction of dietary protein intake should be considered in any child who has undergone a nephrectomy (Thorner et al, 1984). If lower protein diets than those currently employed for children in the clinical setting become implicated, low protein products such as breads, pasta and biscuits will become necessary, possibly in combination with EAA/KA supplements. A crossover comparison of 3 low nitrogen diets (1.65g protein/kg) in infants with a GFR < 6 ml/min/1.73m^2 was conducted by Broyer et al (1983). When half the low protein diet provided by human milk was substituted with EAA, weight gain improved but when the EAA were exchanged for KA, weight gain deteriorated. If KA are to be considered for the treatment of severe

renal failure, approximately 35% of total dietary protein in infants should consist of EAA compared with approximately 20% in adolescents (Yang et al, 1988-89). When a child's dietary protein intake meets, but does not exceed the RNI, it is usually not possible to meet the RNI for all other nutrients without using micronutrient supplements (Raymond et al, 1990). Intakes of vitamins and minerals that are found in relatively high amounts in animal protein foods, such as iron, zinc, calcium, niacin, vitamin B6, B12 and folate are greatly decreased on protein-restricted diets. A separate iron supplement is often required due to the increasing incidence of anaemia with worsening severity of CRI (see section 1.3.8).

Placing a large number of dietary restrictions upon a child, which due to the severity of the restrictions is also required to take a number of probably unpalatable supplements and substitutes over an indefinite time period, is likely to significantly impair their quality of life (Anon, 1975; Baldwin & Falciglia, 1995; Coyne et al, 1995). A higher proportion of the MDRD study patients who were adherent to the diet, liked their eating patterns (Coyne et al, 1995). Poor concordance with advice is likely to be greater with increasing severity of imposed dietary restrictions. Coyne et al (1995) observed that satisfaction with the prescribed eating pattern increased slightly in the usual protein group, declined slightly in the low protein group and declined significantly in the very low protein group. Baldwin and Falciglia (1995) state that taking small incremental steps towards a long-term goal provides a greater chance for success, and lessens vulnerability to lowered self-esteem. As symptoms in children with milder forms of the disease are not apparent, this also increases the difficulties of encouraging children and families to continue to adhere to advice. Feedback, particularly from self-monitoring and from measures of adherence, appears to heighten the effectiveness of intervention efforts (Milas et al, 1995; Gillis et al, 1995). Dietary restrictions resulting in the need for prescribable products will be difficult to justify in the clinical setting unless studies are able to support a significant benefit from severe dietary restriction in forestalling the progression to ESRD by a matter of several years.

1.3.5 Growth and energy intake

Growth failure remains one of the more prominent manifestations of CRI in children, reflected by the fact that more than 50% of the children reaching ESRD exhibit a mean height for age more than 2SD below normal (Betts & Magrath, 1974; Rizzoni et al, 1984). The Paediatric Renal Registry (UK Renal Registry, 2000) shows that approximately 40% of children on dialysis have a height below -2SD of normal, with 21% of the group receiving growth hormone therapy. A reduction in growth velocity is predominantly seen when the GFR falls below 25 ml/min/1.73m^2 (Betts & Magrath, 1974; Schaefer et al, 1996).

Growth can be divided into three phases as described by the Infancy-Childhood-Puberty model (Karlberg, 1989). Each phase depends primarily on a specific determinant of growth. In infancy, nutrition is believed to be the most important determinant, during childhood, growth hormone appears to be predominant, and pubertal growth is primarily dependent on gonadotrophic hormones. Each phase however, can be affected by any factor, and impaired growth at 0.75-1.5 years of age may be related to a partial insensitivity to growth hormone (Karlberg et al, 1996). There is often a delay in pubertal growth spurt, particularly with early onset CRI, but it occurs at a normal age when assessed according to bone age, with a delay in bone age of approximately 2.5 years (Schaefer et al, 1990). A lower pre-spurt height velocity and attenuation of peak height velocity of between 48-58% are frequently observed when compared with late-maturing controls. With this growth pattern, children with CRI from birth enter puberty at stunted heights of > 2 SDS below normal. With delay and blunting of adolescent growth spurt, final height is frequently > 3 SDS below normal (Abitbol et al, 1996).

Retrospective, longitudinal growth and biochemical data were collected in 321 pre-pubertal children with CRI and percentile charts for height and height velocities were constructed (Schaefer et al, 1996). Height velocities were lower in children with a GFR below 25 ml/min/1.73m^2 compared to those with a GFR of 25-50 ml/min/1.73m^2, resulting in a mean height SDS of -2.79 $\pm$ 1.4 SDS and -1.65 $\pm$ 1.5 SDS (age 1-10 years) respectively. Schaefer and colleagues (1996) conclude that GFR appears to be a weak but significant determinant of growth in children with CRI. The NAPRTCS report of registry data for CRI (Fivush, 1998) showed the average child to have a height of 1.5 SD below age- and sex-specific norms and 0.6 SD below weight norms.

Secondary factors such as parental stature also significantly influence growth during each phase (Abitbol et al, 1996). Much of the observed height retardation in mild to moderate CRI has been suggested to be associated with delayed skeletal maturation rather than renal osteodystrophy, the latter only being significant in those with severe CRI (Hodson et al, 1983). Although it is not clear to what extent secondary hyperparathyroidism contributes to growth impairment, it was found to correlate negatively with length growth velocity in infants with CRI (Abitbol et al, 1993). Growth is only arrested completely when secondary hyperparathyroidism results in the severe destruction of the metaphyseal bone architecture. Metabolic acidosis is frequently observed in children with moderate renal failure due to the kidney's reduced ability to excrete ammonia. The severity of acidosis is increased by acid-load from food, such as from excessive ingestion of protein-containing foods, by catabolism and through electrolyte disturbance. Acidosis is associated with growth retardation (West and Smith, 1956), due to stimulation of protein degradation (Williams et al, 1991) and causing a state of growth hormone insensitivity (Brungger et al, 1997). A suboptimal energy intake however, has been suggested to be the most important cause of growth retardation in uraemic children (Chantler & Holliday, 1973).

Anorexia, excessive dietary restrictions and medications, altered taste perceptions (Bellisle et al, 1990; van der Eijk & Allman Farinelli, 1997), substantial hypertension (Caliguini et al, 1963) and intercurrent infections which accentuate loss of appetite, may result in a reduced energy intake [less than 80% of RDA (Betts & Magrath, 1974; Holliday, 1975; Foreman et al, 1996)]. Energy requirements have been suggested to be increased by uraemia (Chantler et al, 1980), although a number of reports in adults suggest that chronic renal failure has no influence on energy expenditure (Monteon et al, 1986; Schneeweiss et al, 1990). Some studies in children have shown that once energy intakes exceeded 80% of the RDA, no association between energy intake and statural growth could be found (Betts et al, 1977; Kleinknecht et al, 1983), whilst other studies have not been able to find any correlation between energy intake and height velocity (Foreman et al, 1996). It is important to prevent loss of growth in the first place, as catch-up growth is rarely seen in children over 2 years of age (Foreman & Chan, 1988). One of the final reports of the GFRD study, which was designed to compare the effect of vitamin D metabolites on renal function, nutrition and growth in 120 children with CRI (Foreman et al, 1996; Chan et al, 1994), included a paper on the

nutritional management of the child with mild to moderate CRI (Sedman et al, 1996). Sedman and colleagues (1996) state that 'prevention of growth failure is much more cost effective than pharmacological therapy' and hence 'assiduous treatment of co-existing renal osteodystrophy and provision of optimal nutritional intake should be accomplished'.

Stunting of growth is especially profound in children with congenital causes of CRI that lead to impaired kidney function in the first few years of life (Jones et al, 1982; Rizzoni et al, 1984), where approximately half of the child's growth occurs during the first two years. Without institution of aggressive therapy measures, these infants are reported to lose as much as 0.4-0.6 SDS /month during the first 6 months of life (Kleinknecht et al, 1983; Rizzoni et al, 1984; Abitbol et al, 1993). Infancy and young childhood are the phases where catch-up in growth has been demonstrated, using nutritional support measures such as nasogastric or gastrostomy tube feeding to achieve, or where necessary exceed, recommended dietary intakes (Claris-Appiani et al 1995; Norman & Evans, 1998; Ledermann et al, 1999; Kari et al, 2000). Not all recent studies have been successful in achieving catch-up growth (Arnold et al, 1983; Abitbol et al, 1993; Reed et al, 1998; Ellis et al, 2001), although this may in part be associated with inadequate nutritional goals. Current recommendations, considered sufficient to promote growth, suggest that children with CRI should be ingesting close to 100% of the RDA for total energy for height-age (Chan, 1973; Hellerstein et al, 1987). Once a growth deficit is established however, additional energy to 125-150% of the RDA may be necessary to achieve catch-up growth (Abitbol et al, 1996), or median weight for chronological age could be used (Reed et al, 1998). Ingestion of excess energy above requirements when growth velocity is consistently zero, will result in excess fat mass.

Serum growth hormone (GH) concentrations are elevated in uraemia, yet growth retardation is common. This is suggested to be due to an apparent GH-resistant state, which is thought to result from a combination of reduced hepatic GH-receptor expression, with subsequent decreased production of insulin-like growth factor-1 (IGF-1) and increased IGF-binding protein levels, which reduce the availability of free IGF-1. IGF-1 is the primary stimulus for the increase in linear growth and it is probable that the reduced production and increased binding of IGF-1 contribute to the GH-resistant state in uraemia (Powell et al, 1997; Tonshoff et al, 1997). Pharmacological doses of

exogenous recombinant human growth hormone (rhGH) [30 IU/m^2/wk or 0.14 IU (0.05 mg) /kg/d] administered subcutaneously have been shown to improve linear growth in children with CRI (Fine et al, 1994; Maxwell & Rees, 1996) and in those on dialysis, particularly during the first year of treatment (Schaefer et al, 1994). The gain in height during subsequent years of rhGH treatment however, is diminished. The magnitude of improvement in linear growth in patients treated with dialysis is not as great as that observed in children with stable CRF (Wuhl et al, 1996). Recombinant growth hormone should therefore possibly be considered in stunted children before they reach the ESRD programme. Use of growth hormone however should not be taken lightly, as it involves a once daily injection until transplantation, which children tend to find traumatic, and it also happens to be a very expensive therapy. Once a successful renal transplant is received, dramatic catch-up growth can occur without rhGH therapy (Grushkin & Fine, 1973), even in pubertal children (Maxwell et al, 1998). Growth hormone has been recommended in children if they exhibit a height or height velocity for chronological age more than 2 SD below normal, but only once correction for insufficient intakes of energy, protein or other nutrients, acidosis, hyperphosphataemia and secondary hyperparathyroidism have been made (NKF-K/DOQI, 2000).

Protein restriction in children with renal disease is often associated with a reduction in total energy intake (Berger, 1977), which is likely to compromise the efficiency of protein utilisation and result in a deleterious catabolism of protein. Raising energy intake enhances the efficiency of protein utilisation and improves nitrogen balance (Munro, 1978; Kopple et al, 1986). Kopple et al (1986) demonstrated that urea nitrogen appearance correlated inversely with energy intake. An increase in carbohydrate foods such as bread, rice, pasta and potatoes are often first- line recommendations, although these foods will increase the intake of protein, albeit of low biological value, and hence not be appropriate for strict low-protein diets. Appetite is often suppressed in more severe renal disease, attributed to the presence of uraemic toxins, alterations in taste acuity, and a reduction in saliva excretion (Chantler & Holliday, 1973), thereby limiting the intake of bulky foods. As a result, more concentrated sources of energy in the shape of fats (Ashworth, 1978) and sugars are endorsed to enable the child to meet their energy requirements. A relative aversion for sucrose however, has been demonstrated in uraemic children when preference tests were performed (Bellisle et al, 1990) and marked anorexia has been noted in uraemic rats when receiving a sucrose-rich diet

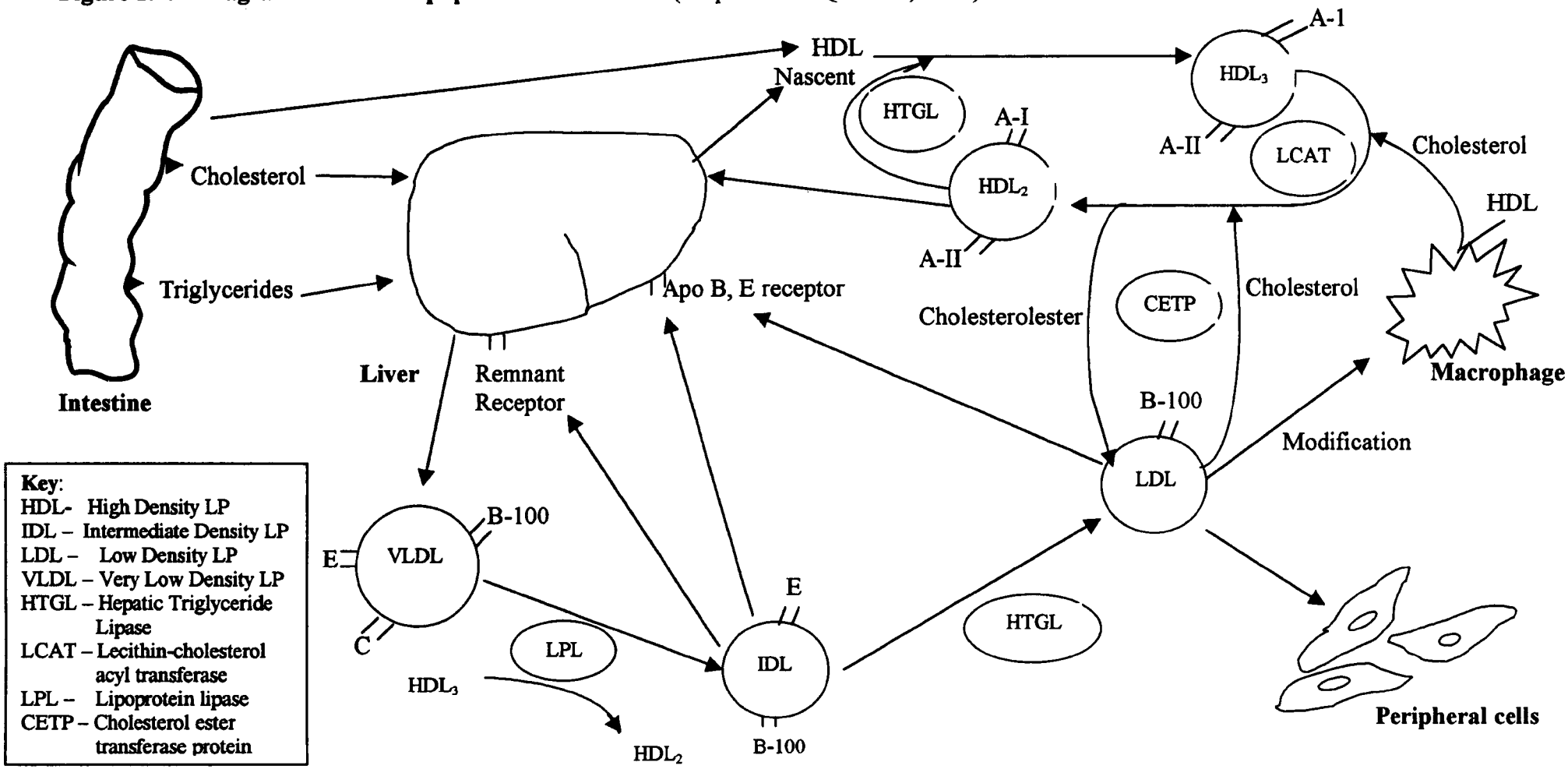
(Kleinknecht et al, 1991). Bellisle and colleagues (1990) attribute this aversion to the metabolism of sucrose producing aversive consequences in children with ESRD, although they do not suggest what these aversive consequences may be.

1.3.6 Hyperlipidaemia and macronutrient intake

The effect of nutritional supplements and additional fats and sugars on lipid profiles requires monitoring, as disorders of lipid metabolism are frequently seen. Figure 1.3.6 illustrates normal lipoprotein metabolism. Dietary lipids are taken up in the intestine, reformed as triglycerides and enter the lacteals where they are known as chylomicrons. The chylomicrons pass through the mesenteric lymph vessels, enter the thoracic duct and join the systemic circulation via the right subclavian vein. These large particles are hydrolysed by lipoprotein lipase (LPL) to core remnants, which are rapidly taken up by hepatic receptors. Water-insoluble lipids are transported in blood by lipoproteins, in which the hydrophobic core consists of triglyceride (TG) and cholesterol esters and the surface coat of protein, soluble phospholipids and unesterified cholesterol. Each lipoprotein has a specific apo-protein composition, which is responsible for the receptor-mediated uptake of lipoproteins in target cells. The endogenous lipoprotein pathway starts with the hepatic synthesis of TG-rich very low-density lipoproteins (VLDL), which contain apo B-100 and apo-E. VLDL are hydrolysed like chylomicrons by LPL in the capillary bed of muscle and adipose tissue, resulting in intermediate-density lipoproteins (IDL). The IDL are part taken up by the apo-B receptor, while other particles are further hydrolysed by hepatic triglyceride lipase (HTGL) in the liver.

The resulting low-density lipoprotein (LDL) is the main cholesterol carrier in blood, delivering cholesterol to peripheral cells. The reverse transport of cholesterol from peripheral cells to the liver is the main function of high-density lipoprotein (HDL). HDL contains mainly protein (apo AI, AII, C, E) and phospholipids. Nascent HDL particles are synthesised in intestine, liver and macrophages. After HDL takes up cholesterol from peripheral cells, the enzyme lecithin cholesterol acyltransferase (LCAT) esterifies cholesterol to cholesterol esters, which are moved to the inner core of the particle resulting in HDL_3. Further uptake of phospholipids and apolipoproteins from the hydrolysis of VLDL results in bigger HDL_2. Cholesterol can be transferred from HDL to other lipoproteins by the action of cholesterol ester transferase protein.

Figure 1.3.6 Diagram of normal lipoprotein metabolism (adapted from Querfeld, 1993)



Defective triglyceride metabolism attributed to decreased activity of the enzymes LPL and HTGL, occurs in the early stages of CRI and is suggested to be the most important abnormality of lipid transport in uraemic dyslipidaemia (Sanfelippo et al, 1977; Attman & Alaupovic, 1991). The down-regulation of LPL has been shown to be completely reversed by parathyroidectomy in animals, suggesting a role of excess parathyroid hormone (Vaziri & Liang, 1997). Hypertriglyceridaemia however, which has been shown to correlate inversely with GFR (Querfeld, 1993; Kari et al, 1998), was not completely ameliorated by parathyroidectomy in animals, suggesting a PTH-independent deficiency of receptor expression (Liang et al, 1998). Children with significant proteinuria have a greater tendency to hyperlipidaemia, associated with an inappropriate production of lipoproteins, namely VLDL, by the liver in response to albumin loss. Excess production of lipoprotein is accompanied by slower than normal metabolism in the peripheral circulation, associated with the reduced activity of LPL due to urinary loss of cofactors (Warwick et al, 1990; Wheeler & Bernard, 1994).

As a result of decreased lipoprotein catabolism, a change in the distribution of lipids within the lipoprotein fraction occurs, with a decrease in HDL cholesterol formation and an increase in VLDL (Zacchello et al, 1987). This is accompanied by a reduction in the major apolipoprotein components of HDL (apoA-I and apoA-II) and an increase in levels of apoC-III which are detectable early in the course of renal disease, before plasma lipid levels increase (Grutzmacher et al, 1988). Deighan et al (2000) noted that 26% of adults with CRI exhibited raised small dense LDL cholesterol concentrations (LDLIII; complex triglyceride-rich apoB-containing lipoproteins), compared to 5% in controls. A strong association between plasma LDLIII and triglyceride concentrations exist, such that those with hypertriglyceridaemia (> 2 mmol/l) had an 86% specificity and 79% sensitivity for predicting LDLIII concentrations of greater than 100 mg/dl (2.6 mmol/l). The combined presence of hypertriglyceridaemia, low HDL, excess small dense LDL and increase in remnant lipoproteins are known as the atherogenic lipogenic phenotype. Low HDL cholesterol (< 1.0 mmol/l) has been shown to be a powerful independent risk factor for the development of cardiovascular disease (Jungers et al, 1997). Increased levels of lipoprotein (a), a cholesterol-rich protein resembling LDL cholesterol have also been noted in children (Querfeld et al, 1993), possibly predisposing them to an increased risk for atherosclerosis and thrombosis.

Samuelsson and colleagues (1997) found that the rate of decline of renal function was significantly associated with baseline concentrations of cholesterol, LDL-cholesterol and apoB in adult patients with CRI. They subsequently noted that complex triglyceride-rich apoB-containing lipoproteins were associated with a higher rate of progression (Samuelsson et al, 1998). The abnormalities in lipid metabolism might be contributing to the progression of the underlying renal disease via such mechanisms as uptake of low-density lipoproteins by macrophages within the glomerulus, and increased production of renal thromboxanes (Keane et al, 1988; Moorhead, 1991).

As additional carbohydrate may exacerbate hypertriglyceridaemia and reduce HDL (Grundy & Denke, 1990), it has been recommended that carbohydrate be reduced and substituted by fat (Chantler et al, 1980). High intakes of saturated fat however, increase serum LDL and triglycerides (Grundy & Denke, 1990). A study by Jureidini et al (1990), using peanut oil supplementation (predominantly mono- and poly-unsaturated fats) did not show any deleterious effects on lipid profiles, suggesting that an adequate energy intake from non-saturated fat sources can improve hyperlipidaemia, perhaps through improved anabolism. Polyunsaturated fatty acids reduce LDL, but also reduce HDL, whereas monounsaturated fats lower both LDL and triglycerides, and are associated with higher levels of HDL (Grundy & Denke, 1990). Chisholm et al (1996) found that the use of a margarine high in mono- and poly-unsaturated fats was preferable to that of butter in lowering LDL cholesterol and apoB in hypercholesterolaemic patients. Diets high in polyunsaturated fats with a reduced carbohydrate intake [35% of total energy (Sanfelippo et al, 1977)] or low-protein intake [0.6g/kg/d (Maschio et al, 1991)] have been provided to adult patients with CRI, with subsequent improvement in their fasting triglyceride levels. D'Amico and Gentile (1993) view a protein restricted diet (0.7g/kg ideal body weight/ day), low in saturated fat, high in monounsaturated and polyunsaturated fat to be of value for partially controlling lipid abnormalities in patients with CRI. They feel that diet has advantages over the pharmacological approach in controlling hyperlipidaemia, in part due to the long-term nature of the condition.

Dietary intervention via restriction of carbohydrate and saturated fat intakes is often not advocated due to the frequently malnourished state of adult uraemic patients (Ritz et al, 1985). For those being treated with a strict low protein diet, low protein substitutes for

pasta, bread and biscuits are necessary to maintain an adequate energy intake, although they tend to be less palatable, require prescription or alternatively need to be purchased at high cost. Children on such diets risk becoming isolated from their peers and family at mealtimes. Querfeld (1993) recommends that there is little place for the dietary treatment of hyperlipidaemia in children with CRI. He emphasises the importance of correction of hypertension and increased physical exercise, with the addition of lipid-lowering drugs for those children with a more atherogenic lipoprotein profile. Kist-van Holthe tot Echten et al (1992a) found that the use of a moderately low protein diet (0.8-1.1 g/kg) and adequate energy intake (100% normal recommendations), obtained through increased use of polyunsaturated spreads and full cream dairy products, prevented the increase in serum total and LDL cholesterol observed in the control group (normal protein intake) over a 1 year period. It would seem appropriate therefore, to recommend limiting saturated fat intake, in favour of a balance of polyunsaturated and monounsaturated fats, as recommended for the normal population (DoH, 1991). Full fat dairy products would not be discouraged due to the lack of a positive association with plasma cholesterol and lipoprotein concentrations (Smedman et al, 1999), or incidence of heart disease (Shaper et al, 1991). Smedman and colleagues (1999) suggest that there are several substances in dairy products, including calcium, lactose, uric acid and conjugated linoleic acid that may be responsible for such effects, but the answer has yet to be elucidated.

Increases in dietary fat and sugar intake often tend to be inadequate to compensate for the reduction in nutritional intake. A prescribable supplement such as a glucose polymer is therefore advocated if the energy intake continues to fall below 80% of the EAR (Foreman & Chan, 1988). In children with CRI whose growth velocity continues to decline despite such oral supplements, early enteral feeding of a nutritionally complete whole-protein feed delivered via the nasogastric or gastrostomy route may be instigated. Claris-Appiani et al (1995) observed increases in both plasma cholesterol and triglycerides following nutritional intervention in children with CRI. Kari and colleagues (1998) however, found that administration of a nutritionally complete feed with a balanced fat and carbohydrate profile similar to published recommendations (DoH, 1991), did not detrimentally affect the serum lipids of children with a GFR between 5-35 ml/min/1.73m^2. Concerns regarding the use of nutritional supplements

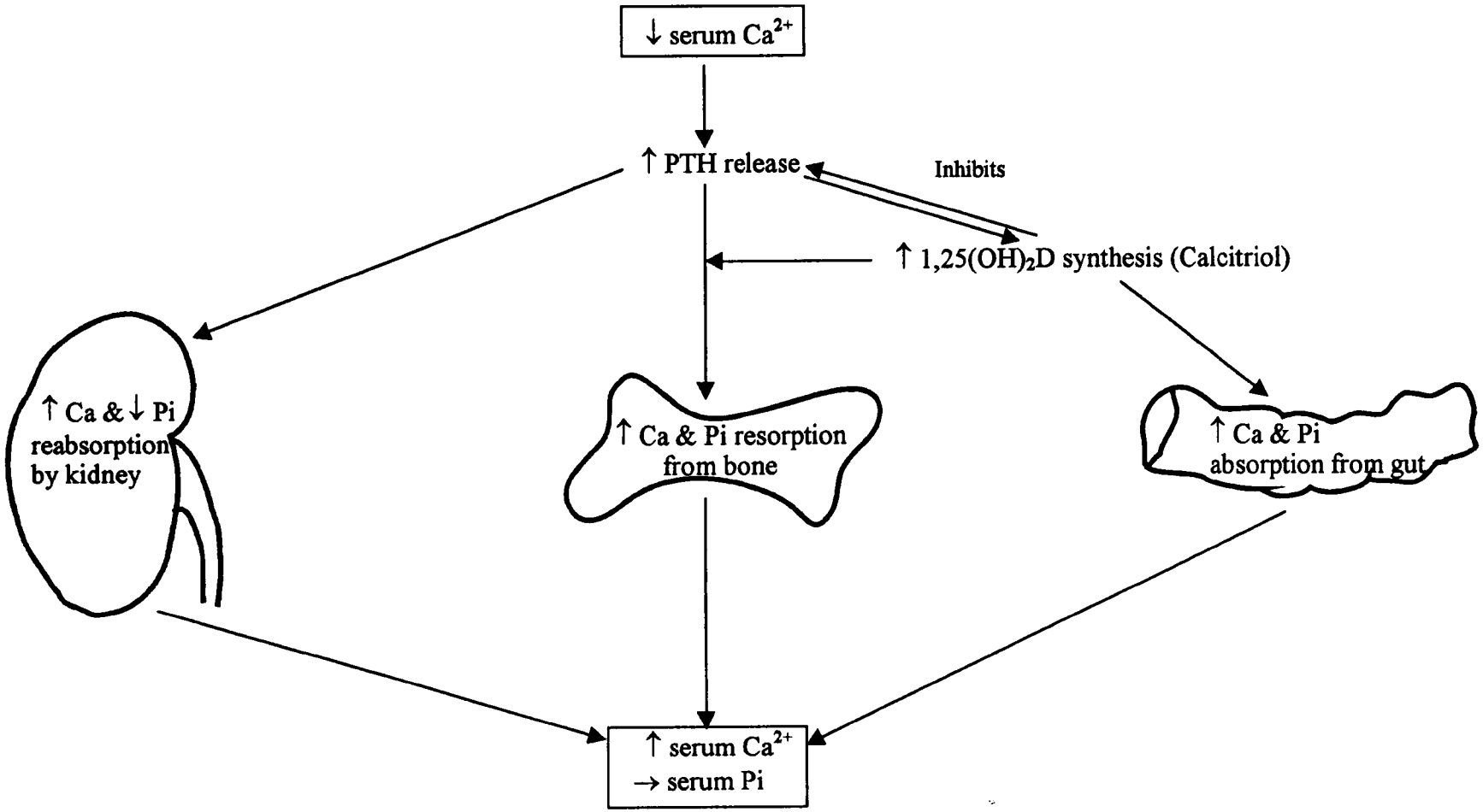
and dyslipidaemia should not preclude their use, due to the greater importance of ensuring adequate nutrition and growth.

1.3.7 Bone metabolism, phosphorus, calcium, and vitamin D

Chronic renal insufficiency in childhood may cause skeletal alterations similar to those seen in nutritional rickets, bone changes associated with secondary hyperparathyroidism, or a combination of both. Renal osteodystrophy develops as a result of the effect of impaired renal function on calcium, phosphorus, vitamin D metabolism and parathyroid hormone (PTH) activity. Evidence of renal osteodystrophy can appear in the bone with only a 50% reduction in GFR, whilst serum creatinine shows little change (Norman et al, 1980).

Calcium is the most abundant cation in the body, with over 99% being associated with bone. Calcium is a basic component of many enzymatic pathways that are critical for internal cellular function. Plasma calcium is composed of 3 fractions; approximately 40% of total serum calcium is protein bound of which 75-90% is bound to albumin, an additional 10% is complexed to various anions and the remaining 50% is free ionised calcium which is the physiologically important component. In the absence of measurements of ionised calcium, laboratories correct the total calcium for changes in protein concentration and changes in pH. Calcium homeostasis is maintained by the interaction between 3 major organ systems; bone, intestine and kidney and is regulated by the principle hormones PTH and 1,25-dihydroxyvitamin D_3 (calcitriol). The calcium sensor receptor mediates the inhibitory effect of calcium on PTH secretion. It is involved in an increased release of PTH from the parathyroid gland in response to a decrease in the extracelluar ionised calcium concentration (Fig. 1.3.7). PTH acts on the kidney to decrease calcium excretion, increase phosphorus excretion and stimulate the production of calcitriol. Calcitriol binds to its vitamin D receptors, and acts on the intestine to promote active absorption of calcium and phosphorus, in bone it increases both bone formation and resorption and inhibits PTH synthesis in the parathyroids. This results in bringing serum calcium levels back to normal, with little effect on serum phosphate concentration.

Figure 1.3.7 The homeostatic response to hypocalcaemia



A negative calcium balance resulting in hypocalcaemia is seen in uraemic patients due to reduced calcium and protein intakes from anorexia, and inadequate absorption of calcium from the gut as a result of impaired activation of vitamin D to its active form, calcitriol (Hellerstein et al, 1987). Secondary hyperparathyroidism develops early in CRI, when serum calcium, phosphate and calcitriol concentrations are normal (Reichel et al, 1991). A hypothesis has been put forward to suggest that an alteration in the calcium sensor receptor of the parathyroid gland may be the earliest abnormality in hyperparathyroidism (Martinez et al, 1996). Circulating levels of calcitriol which directly inhibit PTH secretion are reduced by the time the GFR falls below 50% normal, associated with further elevation in serum PTH concentration (Chan et al, 1994). Nodular parathyroid gland hyperplasia occurs in association with a deficiency of calcium, calcitriol or increase in phosphate, and is accompanied by a loss of calcium and vitamin D receptors, which subsequently result in a reduced ability to detect changes in serum calcium and calcitriol (Gogusev et al, 1997). Significantly higher levels of calcitriol and calcium are therefore required to control the synthesis and secretion of PTH i.e. the threshold of PTH inhibition by extracellular calcium is increased (Brown et al, 1982). Once established, parathyroid hyperplasia has been shown to be poorly reversible (Quarles et al, 1994).

High PTH levels not only contribute to renal bone disease, but in excess, PTH may play a role in the uraemic syndrome (Massry & Smorgorzewski, 1994), may inhibit haem synthesis contributing to renal anaemia (Zingraff et al, 1978; Rao et al, 1993) and contribute to hyperlipidaemia, possibly due to an inhibitory effect of PTH on insulin release and subsequent reduction in LPL activity (Akmal et al, 1990). Serum determinations of calcium, phosphate and alkaline phosphatase are reported to be of little value in the early detection of osteodystrophy, whereas increased intact PTH activity is suggested to be a reliable indicator for commencement of nutritional intervention (Hellerstein et al, 1987).

In adults with ESRD, it has been suggested that maintaining PTH concentrations between 120-250 ng/l (2-4 times the normal range) in those on maintenance dialysis and between 300-375 ng/l in patients immediately pre-dialysis avoids both low and high turnover bone disease (Torres et al, 1995). All patients with a PTH concentration above 450 ng/l showed evidence of hyperparathyroid disease, whereas a PTH concentration

below 120 ng/l was highly predictive of low bone turnover, associated with skeletal resistance to PTH. These values are supported by Salusky et al (1994) for children on peritoneal dialysis who recommend aiming for PTH concentrations of 2-3 times the upper limit of the normal range. Block and colleagues (2000) re-evaluated the risks due to hyperphosphataemia and hyperparathyroidism, particularly associated with the development of cardiovascular disease (cardiomyopathy, fibrosis, atherosclerosis, hypertension and cardiovascular calcifications) as described by Rostand and Drueke (1999), and as a consequence, recommended that PTH concentrations should be maintained between 100-200 ng/l in dialysis patients, which would require more frequent monitoring. In contrast to ESRD, minor elevations of serum PTH concentrations in patients with mild to moderate CRI have been associated with histological lesions of secondary hyperparathyroidism (Hamdy et al, 1995). Treatment in those with mild CRI should not be delayed once serum PTH concentrations reach the upper range of normal (Norris, 1999), in an attempt to prevent nodular parathyroid gland hyperplasia from developing with its associated increase in calcium set-point (Coburn & Elangovan, 1998). Reichel and colleagues (1991) discovered 32% of their patients with a GFR between 60-90 ml/min/1.73m^2 had a PTH concentration above the normal range. Joint medical and dietary management is therefore necessary to ensure an adequate intake of calcium and calcitriol, which together exert a synergistic effect on PTH inhibition, and limit dietary phosphate intake which opposes this action, as early in the course of CRI as possible.

Serum phosphate concentration plays a central role in the development and maintenance of secondary hyperparathyroidism seen in CRI (Slatopolsky et al, 1972). Phosphorus serves as both a regulator of enzymatic activity and as a fundamental source of cellular energy, in the form of adenosine triphosphate. Early in renal insufficiency, normal dietary intakes of phosphate tend to suppress calcitriol production via inhibition of the enzyme 1α-hydroxylase, contributing to a rise in serum PTH levels and more subtle changes in phosphorus levels (Portale et al, 1984). Significant hyperphosphataemia tends not to be seen until the GFR falls below 30ml/min/1.73m^2 (Yang et al, 1988-89). Hyperphosphataemia has been suggested to promote hyperparathyroidism independently of calcium and calcitriol levels (Lopez-Hilker et al, 1990; Kates et al, 1997). Like calcitriol, elevated phosphorus increases the synthesis and secretion of PTH and can also cause parathyroid gland hyperplasia. The mechanism for this is not

yet known, although the effects of hyperphosphataemia may be mediated in part by a decrease in the production of arachidonic acid by the parathyroid cells (Rodriguez, 1999). Kates and colleagues (1997) found that serum phosphorus correlated directly with serum PTH in patients with mild to moderate CRI. Serum phosphate levels above 2.1 mmol/l (6.5 mg/dl) have been linked to a 27% higher death risk for patients receiving at least 1 year of dialysis compared to patients with levels between 0.8-2.1 mmol/l (2.4-6.5 mg/dl) (Block et al, 1998). An elevated calcium x phosphorus (Ca x P) product, which correlates with metastatic calcification was also associated with significantly increased death risk. Patients with a Ca x P product above 72 mg^2/dl^2 had a 34% higher death risk relative to patients with a Ca x P product between 42-52 mg^2/dl^2 (Block et al, 1998). In patients with ESRD, calciphylaxis (calcific uraemic arteriolopathy) has also been reported (Goodman et al, 2000), in association with elevated serum calcium concentrations. Based upon these results, attempts are increasingly being made to lower the Ca x P product to less than 60 mg^2/dl^2 (Norris, 1999).

Dietary phosphate restriction may be beneficial in the early stages of CRI when the serum phosphate level is normal, as it raises serum calcitriol concentration which in turn reduces the level of PTH and subsequent hyperparathyroidism (Portale et al, 1984; McCrory et al, 1987; Brancaccio et al, 1996). This mechanism however, may not operate in severe renal failure because the decrease in renal mass may limit the production of calcitriol (Aparicio et al, 1994), but nevertheless, dietary phosphate restriction may reduce PTH synthesis/secretion directly. Dairy products are particularly high sources of phosphate and protein and hence moderation of these in the diet to provide approximately 800 - 1000 mg phosphorus/day, of which 60-70% of the phosphorus is absorbed, should form part of initial dietary advice (Coleman, 2001). Strict low protein diets can reduce phosphate intake by 50-60% (Hellerstein et al, 1987) but this level of restriction is unpalatable and impractical in children where sufficient protein for growth is necessary.

There is concern in daily clinical practice regarding dairy product restriction resulting in low dietary calcium intakes in children with less severe degrees of CRI, where phosphate restriction is indicated but a calcium-based phosphate binder is not yet required. Kerstetter et al (1998) found that a low dietary protein intake depressed

intestinal calcium absorption in healthy, young women and resulted in hypocalciuria and secondary hyperparathyroidism. Dietary calcium may be a signal to up-regulate vitamin D receptor density at the parathyroids and appears to have a synergistic effect with calcitriol on PTH inhibition and vitamin D receptors in avian parathyroids (Russel et al, 1993). An abnormality in the vitamin D receptor may be present in early CRI (Martinez et al, 1996) such that an adequate dietary calcium intake may be essential in patients with mild CRI (Martinez et al, 1997). Martinez and colleagues (1997) restricted dietary protein and phosphorus in a group of adults with mild CRI and amelioration of hyperparathyroidism was only observed in those who were additionally prescribed a calcium supplement. Phosphate and protein restriction with calcium but not calcitriol supplementation (calcium increased to 1g/d) was also shown to correct hyperparathyroidism in patients with advanced CRI (Combe et al, 1995).

Calcium supplements, often the same as those used for phosphate binders should, unlike the latter, be taken between meals to maximise calcium absorption. It has been suggested that calcium carbonate administered between meals and as a phosphate binder with meals may be an important approach to the management of patients with mild CRI (Martinez et al, 1997). Sanchez et al (1999) recommend a calcium supplement dose of 500 mg/d up to a maximum of 1000 mg/d for adults with renal failure to compensate for impaired absorption of intestinal calcium. No recommendations have been established as yet for children with CRI. The USA guidelines on calcium for healthy children have been updated and recommend an increase in the daily amount advised for children aged 9-18 years from 1200 mg to 1300 mg per day, despite reports that the previous calcium recommendations were not being met (National Academy of Sciences, Food and Nutrition Board, 1997). These guidelines were formulated by estimating the level of calcium intake required to maximise adult peak bone mass, maintain adult bone mass and minimise bone loss in later life. UK current guidelines recommend 800 mg for teenage girls and 1000 mg for teenage boys (DoH, 1991), and the recent report by the committee on medical aspects (COMA) on Nutrition and Bone Health (DoH, 1998) continues to emphasise the importance of achieving these recommendations. The UK guidelines were derived by calculating the theoretical amount of calcium needed for bone growth and for the maintenance of bone mineralisation, and COMA's subgroup do not feel that there is sufficient evidence to justify increasing its recommendations. In the USA, milk and milk products provide 75% of the calcium consumed, compared to

under 60% in the UK due to the statutory fortification in the UK of white flour and therefore bread with calcium, which continues to be advocated in COMA's recent report. A possible link between osteoporosis and salt intake is also acknowledged, with high salt intakes being reported to increase calcium excretion.

Dietary restriction alone is often not sufficient to maintain a normal serum phosphate concentration, and if nutritional intake is adequate, there is almost always a requirement for a phosphate binder by the time renal function reaches approximately 30% of normal. Phosphate binders can only prevent the absorption of a proportion of the dietary intake and therefore a low phosphate diet remains imperative (Delmez, 1992). The normal range for plasma phosphate decreases throughout childhood and should be kept within 2 standard deviations of the mean (Renal Association, 1997). In adults this refers to an upper range serum phosphate of 1.7 mmol/l. Data from both Lowrie & Lew (1990) and Block et al (1998) would suggest that an increase risk of death did not occur until serum phosphate concentrations exceeded 2.1 mmol/l, and that those patients with a serum phosphate level between 1.7 – 2.1 mmol/l had a better prognosis than those with a lower serum phosphate. Lower serum phosphate concentrations may be a reflection of poor dietary intake and malnutrition, in the same way that an increased risk of death is observed in those patients exhibiting the lowest serum cholesterol concentrations (Lowrie & Lew, 1990).

In the past, aluminium hydroxide was the phosphate binder of choice until it became clear that aluminium toxicity could occur. Calcium carbonate is currently one of the most commonly used binders, serving a dual role: it binds dietary phosphate in the intestine and because it is 40% elemental calcium by weight, helps to supply the recommended calcium requirement in the diet. It is estimated that approximately 20-30% of the calcium load is absorbed. The starting dose is 10-20 mg elemental calcium/kg/d and is subsequently increased until the desired serum level is obtained; preferably a serum phosphate level at the lower limit of the normal range for age (Yang et al, 1988-89). Tsukamoto et al (1995) demonstrated that calcium carbonate administration significantly lowered serum PTH and alkaline phosphatase levels without affecting serum calcitriol concentrations in patients with mild to moderate CRI. Alternative calcium-based phosphate binders such as calcium acetate have been proposed as a means of providing less calcium for a similar phosphate-lowering effect

to help minimise hypercalcaemia (Schaefer & von Herrath, 1993). Patients should chew calcium carbonate or swallow calcium acetate preparations several minutes before meals on an empty stomach, as a low pH allows for optimal dissolution of the calcium salts and optimal phosphate binding (Janssen et al, 1996). It is also prudent to remember that phosphate binders have a tendency to impair the absorption of other micronutrients such as iron and hence micronutrient preparations are best not taken at the same time as phosphate binders. This is likely to be of significance in those children requiring overnight feeding using complete nutritional supplements with the addition of a phosphate binder to the feeding bag.

The long-term efficacy of calcium based agents continues to be questioned, associated with poor adherence to medication (Curtin et al, 1997) and a high incidence of hypercalcaemia (Sperschneider et al, 1993) which may result in metastatic calcification. Calcium-free phosphate binders such as magnesium hydroxide (Oe et al, 1987) however, are likely to result in other complications such as diarrhoea and hypermagnesaemia. New agents such as RenaGel®, a non-absorbed cationic polymer; poly[allylamine hydrochloride] (Slatopolsky et al, 1999) or zirconyl chloride octahydrate (Graff & Burnel, 1995) may overcome some of the limitations of phosphate binding therapies, although in practice, a greater number of Renagel capsules are required to achieve a similar phosphate binding effect to that of calcium carbonate/acetate. Renagel however, is now available in the USA as double strength caplets, which is likely to improve compliance with this medication. Chertow et al (1999) compared the use of Renagel alone with Renagel plus a nightly dose of calcium (900mg elemental calcium). Serum PTH concentrations were only significantly decreased in the Renagel plus calcium group, although both treatments proved to be similarly effective in the treatment of ESRD-related hyperphosphataemia. They would therefore recommend the addition of calcium to the patient's diet to meet the RNI, if the patient was not overtly hypercalcaemic or had a raised calcium x phosphate product. Chertow and colleagues (1999) also found a decrease in LDL cholesterol of 30% and increase HDL cholesterol of 18%, which may prompt its use in certain patients.

The reduced rate of conversion to the active form of vitamin D in conjunction with resistance of the intestine to the actions of vitamin D in CRI, often necessitates supplementation with vitamin D preparations to increase calcium absorption in the gut,

ameliorate renal osteodystrophy and promote growth. Patients with mild CRI have histological abnormalities associated with increased PTH activity despite normal to mildly elevated serum PTH and normal serum calcium concentrations (Hamdy et al, 1995). The optimum time to initiate therapy with active forms of vitamin D is therefore felt to be at the onset of secondary hyperparathyroidism or when the GFR decreases below 50% of normal for age in children (Portale et al, 1984; Chan et al, 1994). Active forms of vitamin D include calcitriol, dihydrotachysterol and 1-alpha-hydroxyvitamin D_3 (alfacalcidol). Calcitriol and dihydrotachysterol have been shown to be equally potent in suppressing PTH elevation (Chan et al, 1994). The PTH response to calcitriol treatment however, is poor when serum phosphorus is high (Quarles et al, 1994) and hence provides further support to the importance of maintaining a low dietary phosphate intake. When administered orally or parenterally, careful monitoring of serum calcium is necessary as hypercalcaemia and hypercalciuria may cause metastatic calcification and possibly accelerate the course of renal deterioration (Foreman & Chan, 1988; Yang et al, 1988-89). Ritz and colleagues (1995) demonstrated that low-dose calcitriol (0.125μg/d) blunted the deterioration of hyperparathyroidism in adults with moderate CRI without causing hypercalcaemia, hypercalciuria or hyperphosphataemia. No significant deterioration in GFR was demonstrated between two groups of 8 children with moderately impaired renal function when receiving a dose of 10 ng/kg/d of alfacalcidol or 670 ng/kg/d of calciferol (Eke & Winterborn, 1983). Calcitriol has been demonstrated to be associated with a more rapid rate of deterioration of renal function than dihydrotachysterol and thus, along with considerations of cost-effectiveness, Chan et al (1994) recommend dihydrotachysterol over calcitriol as the treatment of choice in children with CRI.

As with the new phosphate binding agents, new vitamin D analogues are also being developed, such as paricalcitol [19-nor-1α, 25-dihydroxy vitamin D_2 (Zemplar injection, Abbott Laboratories)], trialed in a multicentre study on 35 adults patients with ESRD (Llach et al, 1998), 22-oxacalcitriol (Chugai Pharmaceuticals) and the inactive prohormone doxercalciferol (1α-hydroxyvitamin D_2; Hectorol Gelcaps, Bone Care International). These new analogues are designed to inhibit PTH synthesis without any significant effects in the bone or gut, such that PTH inhibition can be achieved without hypercalcaemic or hyperphosphataemic side effects. For those patients with hypercalcaemia and a Ca x P product above 60 mg^2/ ml^2, products such as allosteric

calcium receptor agonists (calcimimetics), i.e. they mimic the action of calcium, are currently under development as they may be suitable alternatives in limiting PTH secretion (Antonsen et al, 1998).

Overly aggressive treatment of renal osteodystrophy with vitamin D therapies and calcium salts appears to have increased the number of patients with adynamic bone disease, characterised by a decrease in bone turnover (Malluche, 1995). This is associated with a tendency towards hypercalcaemia, ageing of the bone due to diminished bone remodelling and possibly impaired repair of microfractures, increasing the risk for fractures. Adynamic bone disease is commonly associated with moderately elevated serum PTH concentrations compared to those with normal renal function, but lower than those with secondary hyperparathyroidism. This is likely to be associated with variations in functional parathyroid gland mass rather than disturbances in calcium receptors in the parathyroids (Goodman et al, 1997). Adynamic bone disease was shown to develop in children receiving peritoneal dialysis with secondary hyperparathyroidism following intermittent calcitriol therapy (Goodman et al, 1994). Marked reductions in PTH were noted, suggestive of adynamic renal osteodystrophy but reduced bone formation and turnover was also noted in some patients with secondary hyperparathyroidism, suggesting that calcitriol might in part directly suppress osteoblastic activity and thus contribute to adynamic bone disease. The same group have recently demonstrated diminished linear growth in pre-pubertal children, particularly in those with the adynamic lesion, during high dose intermittent calcitriol therapy whilst undergoing peritoneal dialysis (Kuizon et al, 1998). It is suggested that the therapeutic administration of calcitriol can directly affect epiphyseal growth plate chondrocytes, resulting in reduced linear growth.

In contrast, the under-dosing of calcitriol may also contribute to the development of hypercalcaemia and hyperphosphataemia (Llach & Yudd, 1998), due to the decrease in vitamin D receptors in the parathyroid glands of uraemic patients. Low doses of calcitriol may be insufficient to modify PTH secretion, yet sufficient to raise serum calcium and phosphorus concentrations via increasing absorption in the gut and release from the bones. The use of serum PTH levels to monitor bone activity, although the most clinically sensitive indicator available, should thus be used with caution, taking care to avoid over and under-suppression of parathyroid gland function.

1.3.8 Anaemia and Iron

Originally, the anaemia of CRI was categorised as a non-specific anaemia of chronic disease (Eschbach & Adamson, 1985) which later became recognised as being normocytic [normal mean corpuscular volume (MCV)] and normochromic [normal mean corpuscular haemoglobin concentration (MCH)] in nature. Predominantly, renal anaemia is associated with depressed erythropoietin (EPO) production. EPO is a glycoprotein hormone that regulates the rate of proliferation and differentiation of erythroid precursors in the bone marrow in response to anaemia or hypoxia, whose principal site of production (approximately 90%) is the kidney. Other factors associated with renal anaemia are chronic blood loss, usually from the gut or uterus, inflammation or infection (Macdougall et al,1992a), iron and/or folate and vitamin B12 deficiency (Klemm et al, 1994), hyperparathyroidism (Zingraff et al, 1978; Rao et al, 1993) and shortened red blood cell survival with haemolysis (Evers, 1995). In children, a linear relationship between haematocrit and GFR has been demonstrated but significant anaemia tends to be only seen when the GFR falls to less than 20 ml/min/1.73m^2 (Chandra et al, 1988).

Currently there is debate as to when to treat renal anaemia, which is a major stimulus to the development of left ventricular hypertrophy (LVH). LVH is a major risk factor for ischaemic heart disease, cardiac failure and sudden death; being prevalent in about 75% of adult patients starting dialysis (Foley et al, 1995). Foley and colleagues (1993) stated that for every g/dl decrease in haemoglobin concentration, the relative risk of mortality increased by 18%. Levin and colleagues (1999) discovered that 36% of adults with varying levels of CRI presented with LVH, and a reduction in haemoglobin of 0.5 g/dl over one year resulted in a 32% increase in left ventricular growth. The Working Party for European Best Practice Guidelines (ERA/ EDTA, 1999) and the National Kidney Foundation Dialysis Outcomes Quality Initiative (NKF-DOQI, 1997) for the treatment of anaemia recommend that an anaemia assessment for patients with CRI should be commenced when the haematocrit falls to <33% (haemoglobin (Hb) < 11 g/dl) in pre-menopausal females and pre-pubertal patients. This value represents approximately 80% of the mean normal Hb concentration for these types of patients. There is a suggestion that renal anaemia should be prevented from developing in the first place and an ongoing UK multicentre 'early intervention' study aims to assess this (Macdougall, 1999).

Iron deficiency anaemia is one of the most common states of deficiency in man, particularly affecting infants, children and women (Oski, 1993). The National Diet and Nutrition Survey of young people aged 4-18 years (Gregory & Lowe, 2000) found that the average intake of iron met the RNI for boys, but only met 82% RNI for iron in girls and the mean intake for girls aged 15-18 years was only 58% RNI. This in part may be a reflection that the RNI for girls is higher than that for boys to account for menstrual losses. The proportion of intakes of iron below the lower reference nutrient intake (LRNI) for older girls was much higher than for boys; 45% of 11-14 year olds and 50% of 15-18 year olds compared to 3% in boys and younger girls. The major sources of iron were derived from cereal products such as white bread and breakfast cereals, both of which are fortified with iron. Of the oldest girls, 9% were anaemic (Hb < 11g/l) and 27% had low iron stores (serum ferritin levels < 15μg/l). The same survey in children aged $1^1/2$ to $4^1/2$ years (Gregory et al, 1995) reported one eighth of the youngest children and a twelfth of all children to be anaemic, and serum ferritin concentrations <10μg/l were demonstrated in 20% of children.

Chronic renal insufficiency may exacerbate iron deficiency if iron chelators such as phosphate binders are administered, or requirements for iron are increased in association with the use of recombinant human erythropoietin (rhuEPO). Each child should be advised on those foods rich in iron, particularly meat, which contains haem iron bound to porphyrin. This is absorbed intact, is highly bioavailable and tends to stimulate absorption of iron from other foods (Finch, 1994). Healthy children are encouraged to consume iron fortified breakfast cereals as they are a significant source of non-haem iron (McNulty et al, 1996), and as such should also be encouraged in children with CRI. Non-haem iron should preferably be accompanied by a source of vitamin C which can up to double the absorption of iron (Oski, 1993). Vitamin C is required for conversion of ferric iron to its ferrous state, which is necessary before absorption across the gut mucosa can occur. Dietary chelators of iron such as tannins in tea (Disler et al, 1975) and phytates in fibre should be restricted. Calcium in the form of dairy products such as milk and cheese may inhibit iron absorption by between 30 and 50%. It has been suggested that milk would be best avoided as a drink at the two largest mealtimes in an attempt to separate iron and calcium intakes (Gleerup et al, 1995). Long-term supplementation with calcium in adolescent girls however, was not found to affect iron status as assessed by serum ferritin and red blood cell indices (Ilich-Ernst et al, 1998).

The body may adapt to calcium intake and improve the efficiency of iron absorption, and hence it has been recommended that calcium-rich foods do not need to be avoided during meals containing the majority of the day's iron intake (Minihane & Fairweather-Tait, 1998). Dietary advice should be aimed at achieving the RNI for iron (DoH, 1991) and should be sufficient for children with mild CRI who would not be expected to be anaemic in association with their renal condition.

Children exhibiting iron deficiency anaemia usually require a therapeutic course of oral iron to correct the deficiency, although compliance can be poor due to its taste, or through causing gastrointestinal upsets such as bloating, constipation or diarrhoea. Iron preparations tend to turn stools black and patients should be warned of this prior to commencement, to aid compliance. Attempts to improve dietary intake prior to the development of iron deficiency anaemia are therefore preferable. There are a number of oral supplements available, which include ferrous sulphate, an inorganic salt (200mg providing 65mg elemental iron), and ferrous fumarate (200mg providing 65mg elemental iron) and gluconate (300mg providing 35mg elemental iron) which are organic salts. A polysaccharide-iron complex (1 capsule providing 150mg elemental iron) is also available. Ferric salts are reported to be absorbed less well. The NKF-DOQI guidelines (1997) recommend that a daily dose of at least 200 mg elemental iron for adults or 2-3 mg/kg for children is necessary to maintain adequate stores and prevent iron deficiency, given in 100mg doses two to three times a day. Doses greater than 400mg daily may cause nausea and vomiting. Oral iron therapy is much less well tolerated by children, especially in relation to constipation. Further studies have been recommended to investigate the potential mucosal damage caused by iron sulphate and its role in the production of carcinogens that may be linked with the development of colorectal cancer (Lund et al, 1999).

Oral iron is best absorbed when ingested without food or other medications, particularly calcium salts. The bioavailability of iron ingested within 2 hours of food or 1 hour after, is decreased by up to 50% (Piraio-Biroli et al, 1958). Iron ideally, should be prescribed two hours after a meal. Coated iron supplements and time-release tablets bypass the site of optimum iron absorption, the upper duodenum, and hence are best avoided. Vitamin C has been shown to increase elemental iron absorption, the effect being close to log dose-dependent, indicating that most benefit is obtained by relatively

small amounts of ascorbic acid, of around 50 mg per day in the meal (Hallberg et al, 1989). Some manufacturers add vitamin C to their iron supplements. Increasing vitamin C intake above 100-150 mg per day however, would not be advocated in renal patients due to the increased risk of oxalate formation.

A number of children with severe CRI and a majority of children with end stage renal disease fail to respond to high dose oral iron supplementation alone (5 mg/kg/d) and require administration of rhuEPO. The NAPRTCS study for CRI (Fivush, 1998) demonstrated that 26% of the children conservatively managed received oral iron, and 13% were on rhuEPO therapy. The NKF-DOQI (1997) guidelines suggest that if there is no cause for anaemia other than CRI (all the markers for iron deficiency are normal i.e. normocytic, normochromic anaemia) and serum creatinine is above 177 μmol/l (2 mg/dl), the anaemia is most likely to be due to EPO deficiency. The starting dose of rhuEPO in children on dialysis without inducing side effects is suggested to be between 50-150 IU/kg/wk, in 2-3 divided doses IV or subcutaneously (Van Damme-Lombaerts & Herman, 1999). In predialysis patients where renal anaemia is usually less severe, a starting dose of 25-50 IU/kg/wk in 1-2 doses subcutaneously is recommended. Subsequently, the dosage can be titrated in steps of 50 IU/kg/wk IV or 25 IU/kg/wk subcutaneously. Children younger than 5 years of age appear to have a greater requirement for rhuEPO per unit body weight and may need up to 300 IU/kg/wk (Jabs et al, 1994). Subcutaneous administration can be distressing, particularly for the younger child, and for children on peritoneal dialysis, rhuEPO can be administered in a small volume of dialysis fluid (50 ml bags) during the daytime dwell, providing similar bioavailability to that after subcutaneous administration, with a mean dosage of approximately 200 IU/kg/wk (Reddingius et al, 1997). Weiss and colleagues (2000) have demonstrated that administration of once weekly subcutaneous rhuEPO can be as safe and effective in maintaining Hb concentrations in stable haemodialysis patients, as two or three times weekly administration of the same total dose. Recently an erythropoietin analogue has been developed; Novel Erythropoiesis Stimulating Protein (NESP), which is a hyperglycosylated erythropoiesis-stimulating protein with a presumed three-fold longer terminal half life than rhuEPO in man (Macdougall et al, 1999). These alternatives may have a role to play in reducing the number of injections required for children and improve overall compliance.

The goal is to increase the haemoglobin concentration at a rate of 0.2-0.5 g/dl per week and the European best practice guidelines for anaemia (ERA/ EDTA, 1999) recommend that the target should be for at least 85% of patients to have a Hb concentration greater than 11 g/dl (haematocrit > 33%). If this minimum is attained, it is likely that the mean for the total population will be 12-12.5 g/dl. It is an incomplete correction of anaemia however, and controversy exists as to whether patients would further benefit from normalisation of Hb concentrations. There is concern that patients with cardiovascular disease have an increased risk of death if a normal haematocrit is achieved (Besarab et al, 1998) and hence for these patients, the European guidelines recommend keeping the Hb concentration within the range of 11-12 g/dl. Several large multicentre studies have been set up to examine target Hb concentrations, including the US (Amgen) study, the Scandinavian trial and the Canadian trial, the results of which are not yet available (Macdougall, 1999).

Iron deficiency (Eschbach et al, 1989), infections (Macdougall et al, 1992a; Gunnell et al, 1999) and hyperparathyroidism (Mandolfo et al, 1998) are the most common causes of sub-optimal response to rhuEPO therapy. It is important to maintain adequate serum iron concentrations, since rapid erythropoiesis can lower serum iron concentrations even in the presence of total body iron overload. Iron deficiency may be absolute, when total body iron stores are exhausted, or functional, when there are ample iron stores but there is failure to release iron rapidly enough to satisfy the demands of the bone marrow. In the body, 75% of iron is functional, the majority of which is in haemoglobin, with approximately 1% being bound to transferrin. Transferrin carries and donates iron to the sites of haemoglobin synthesis and as such is a marker of functional iron deficiency. The other 25% of iron is stored, primarily as ferritin and hence serum ferritin levels indicate the degree of absolute iron deficiency. The serum ferritin concentration is directly proportional to the size of the body's iron store (Siimes et al, 1974), although inflammatory processes may also elevate it. The assessment of iron status in children with CRI is described in section 2.3.

Oral iron is often inadequate to meet the high turnover of red cell production within the bone marrow in many patients receiving rhuEPO. This is due to a combination of poor absorption from the gut, poor bioavailability and poor compliance (Macdougall, 1999). Consequently, intravenous iron, which provides adequate iron quickly, has been

increasingly used in patients receiving rhuEPO. Adequate body iron stores are even more crucial in children than in adults for allowing a rapid and full response to rhuEPO (Morris et al, 1994). The intravenous (iv) administration of iron may be necessary when rhuEPO therapy is initiated, if iron status is not maintained on oral iron (plasma ferritin <100ng/l, transferrin saturation <20% and/or percentage hypochromic red cells >10%) or an intolerance to oral iron is present (ERA/ EDTA, 1999). A reduction in the dose of rhuEPO required has been observed in patients on iv iron compared to those on oral iron (Fishbane et al, 1995). High-dose, medium-dose and low-dose regimens exist for giving iv iron, dependant in part on their medical management. The low-dose regimen (20-60mg iron) is used for haemodialysis patients where a dose is given at each treatment session, the medium dose (100-400mg) is given as a single dose, and the high-dose regimen (500-1000mg) can only be given if using iron dextran, which is the most stable preparation but carries a risk of anaphylaxis. The stable polynuclear ferric hydroxide sucrose complex has the lowest toxicity (Faich & Strobos, 1999) and is the first choice for parenteral iron therapy for children (Van Damme-Lombaerts & Herman, 1999). A 5 ml vial contains 100 mg ferric iron and doses of 2-7mg iron/kg/wk in children are given slowly over at least 30 minutes. Iron given orally three times a day between meals may be adequate to maintain iron status when lower doses of rhuEPO are used during the maintenance phase of treatment (Eschbach et al, 1989). Concerns exist over iron toxicity and the ability of excess iron to increase quantities of hydroxyl radicals, thereby increasing oxidative damage in patients with infection and also inhibiting phagocytosis. Although a large multicentre trial failed to show a relationship between infection rates and serum ferritin concentrations (Hoen et al, 1998), the European Guidelines for anaemia recommend 800 μg/l ferritin as the safe upper limit (ERA/ EDTA, 1999).

The introduction of rhuEPO has resulted in a significant reduction in the use of blood transfusions and thus a reduction in the relative risk from such a procedure and a decreased sensitisation for children on renal transplant waiting lists. Eschbach and colleagues (1989) observed the use of rhuEPO in adults with severe CRI, who did not yet require dialysis, and noted that all patients reported an improvement in appetite, activity level and sense of well-being following correction of their anaemia. Significant benefits have been reported with the correction of anaemia in children on dialysis, including improved appetite, school attendance, a reduction in the frequency of non-

specific complaints (Sinai-Trieman et al, 1989) and improved exercise tolerance (Montini et al, 1990). A review by Jabs (1996) however, concluded that correction of anaemia by rhuEPO has not been shown to improve the growth of children with CRI.

Recombinant human erythropoietin was found to be effective in correcting the anaemia of adult patients with progressive renal failure without affecting renal function, although it was suggested to be associated with an increase in blood pressure (Eschbach et al, 1989). The most likely factor responsible for rhuEPO-induced hypertension is an increase in systemic vascular resistance caused by an increase in serum viscosity or loss of hypoxic vasodilatation (direct vasoconstrictor effect) (Buckner et al, 1990). Krmar and colleagues (1997) demonstrated that long-term administration of rhuEPO in children pre-dialysis was not associated with accelerated deterioration via inducing hypertension, but actually delayed deterioration of renal function. They recommend that rhuEPO should be commenced in all anaemic children pre-dialysis, perhaps with the exception of those characterised by a rapidly progressive course or severe hypertension (Scharer et al, 1993). Complications of rhuEPO administration other than hypertension may include hyperphosphataemia and hyperkalaemia (Alexander, 1991).

1.3.9 Improving adherence to dietary advice

Most of the literature has focused on the term compliance, commonly defined as the extent to which a person's behaviour (in terms of taking medications, following diets or making other lifestyle changes) coincides with the medical advice prescribed (Haynes, 1979). The term adherence, defined in a dictionary as 'behaviour in accordance to' is often used interchangeably with compliance. Many factors influence adherence, including the complexity of the recommendations, environmental and social circumstances, the quality of participant-professional interaction and the techniques used to counsel and teach the participant (Milas et al, 1995; Gillis et al, 1995; Baldwin & Falciglia, 1995).

The terms compliance and adherence imply that a patient takes orders from a health professional. Appreciation of the concept of concordance is becoming recognised to be important in the successful management of patients. Concordance is where an agreement is reached after negotiation between a patient and healthcare professional

who respects the beliefs and wishes of the patient, in determining whether, when and how medicines and other treatments are to be taken (Dickinson et al, 1999). Non-adherence is common, tends to increase over time and can be partial or intermittent (Butler & Cairns, 2000). A collaborative educational approach to tackling the problem of non-adherent behaviour can be achieved by adopting a problem-solving stance in which the patient collaborates to solve the problem (Turk & Kerns, 1985).

Food choice varies, depending on age, and hence dietary advice needs to be delivered in a different way, depending upon the age of the child. The 'terrible two's' is a period often associated with food refusal and faddy eating, where the child starts to exert their independence and demand attention in all manner of ways (Wardley et al, 1997). This is readily exacerbated by periods of illness and it can be very difficult for mothers to establish an adequate dietary intake and acceptable eating behaviour following these periods (Batchelor, 1999). There is a risk that food intake may be over-reported by mothers, in an attempt to give the impression that they are feeding their child adequately. For healthy children under 5 years of age however, food diary records have been considered to be reasonably representative of true intake (Black et al, 1993; Nelson et al, 1989). There is a lot of pressure on mothers to ensure that their child gains weight appropriately, which will be confounded by the restrictions placed on foods that can be given to a child with CRI. From clinical experience, young children who are chronically ill or lack an appetite often seem to choose to drink milk and eat yogurts and cheese in preference to other foods, supposedly because they are bland and smooth in texture. Unfortunately, it is these very foods that are usually restricted first due to being high sources of protein, phosphate and salt and advice will need to be delivered in an empathic and practical manner, ensuring that total energy intake is not compromised.

Reliability of food intake records tends to decrease with increasing age, as children eat more meals away from home and the responsibility for reporting food intake shifts from the parent to the child (Black et al, 1993). Methods for assessing the accuracy of food diary reports are described in section 2.1. Food choice increases with age, particularly if the child is able to chose its own meal at school, and children become increasingly susceptible to peer pressure. From clinical experience, parents often give packed lunches instead, to exert some control over their child's food intake in an attempt to improve adherence to the dietary prescription, although there is no guarantee that this is

what was eaten. Snacking or 'grazing' is a common pattern of eating in adolescents, which more often than not comprises of crisps, biscuits, confectionery and carbonated drinks (Gregory et al, 2000). There are also social pressures for adolescents, with the media exerting a large impact on self esteem and body image, with emphasis on having a slim figure if a girl, and developing a muscular physique if a boy (Andersen et al, 1995). This is of particular concern in children with chronic illnesses where they often cannot afford to lose body weight and their priorities may not match the objectives of the paediatric renal team. It is of particular importance in these instances that a concordant approach is taken.

Adherence to nutrition therapies for chronic renal disease is particularly challenging because multiple nutrient modifications are often prescribed and must be maintained throughout the patient's life (Miller & St. Jeor, 1980). These authors felt from their review that inadequate compliance with prescribed low protein, low phosphate diets in adults with renal failure may have played a role in predisposing them to malnutrition. When children are placed on any restrictive, disruptive diet, psychosocial difficulties and feeding problems can result. In the younger child, increasing energy intake by dietary manipulation is much more than provision of a dietary regimen, as appetite is already poor and attempts to 'force feed' can create further food aversion (Chantler & Holliday, 1973). 'Using special dietary products and not being able to eat like peers can make children feel 'different' and stigmatise them' (Raymond et al, 1990). As the child gets older and is required to take on some of the responsibilities themselves, conflict at home can occur. Adolescent renal patients have reported lowered self-esteem related to family conflict associated with their growing independence (Davis et al, 1996). Poor psychological adaptation resulting from these problems has been linked to non-adherence. Energy, vitamin and mineral intakes as a percentage of RDA for age have been shown to decrease with increasing age in children with CRI, which may reflect the greater parental control over the intake of younger compared to older children with CRI (Foreman et al, 1996). Non-adherence to prescribed vitamin and mineral supplements and special dietary products may result in poor nutritional status and growth. To help prevent deterioration of nutritional status and maintain satisfactory growth rates, regular assessment, nutrition counselling and monitoring are essential (Hellerstein et al, 1987).

A leading article in the BMJ in 1975 quoted that 'Imposition of an unpalatable diet solely in an imperious attempt to improve the biochemical profile is neither reasonable nor kind' (Anon, 1975). Low protein diets can be difficult to adhere to and for this reason substantial dietetic time has been invested in studies involving low protein diets, in an attempt to achieve the target protein intakes (Dolecek et al, 1995; Rosman et al, 1984). Low sodium diets are also difficult to adhere to, particularly concerning adolescents (Sinaiko et al, 1993). It has been suggested that the magnitude of dietary change (sodium reduction) in adult renal patients may be more important in reducing blood pressure than attempting to achieve a target figure (Levey et al, 1995). This helps to substantiate the importance of adopting an individualised approach for education, rather than aiming to achieve a set nutrient target level for the general population.

Korhonen et al (1999) set out to investigate adherence to salt restriction and its effects on blood pressure in 39 adult subjects with mild to moderately elevated blood pressure. They participated in a placebo controlled study on the effects of salt restriction alone or in combination with an ACE inhibitor, which involved a 4 week run-in period on their normal sodium diet and placebo ACE inhibitor, thereby acting as their own controls. For the next 8 weeks they followed a low salt diet (5g per day) and were then randomised into a low salt diet with either a placebo or an ACE inhibitor for a further 12 weeks. The subjects were provided with oral and written instructions by a dietitian on how to choose and prepare food to reduce their salt intake. A low sodium bread (0.5%) was supplied free of charge and they were advised to use 50% less salt than normal in cooking and baking. They were asked to eat low sodium alternatives of meat and fish products, cereals and dairy products and they also participated once or twice in group meetings during which time they prepared dishes without salt. They met with the dietitian at every visit (baseline, 4, 12, 18 and 24 weeks). Four day semi-quantitative food diaries were done 3 times, before weeks 4, 12 and 24 and 24 hour urinary sodium excretion, blood pressure and body weight were determined at every visit. Despite the intense support, only 20% of subjects were able to reduce their salt intake to under 5 g / day. Those who were successful tended to be motivated home living, female subjects. The main reason given for the differences between men and women (47% women, 8% men) was due to the lower energy intake of women. Despite the fact that the target was not achieved by many, salt intake did significantly reduce, as noted by both food diaries and urinary sodium excretion (although there was poor correlation between the two),

and was accompanied by a significant reduction in blood pressure. They attribute their success compared with other studies (Alli et al, 1992; Elmer et al, 1991) to specialised dietetic support, a supply of low salt bread and regular follow-up contacts.

Long term adequate suppression of secondary hyperparathyroidism was achieved in pre-dialysis uraemic children using a simple regime of high-dose phosphate binders (calcium carbonate, mean of 97 $\pm$ 46mg /kg) with meals, and a mild dietary phosphate restriction (approx. 600mg phosphorus per day) involving restriction of milk, cheese and yogurt (Tamanaha et al, 1987). A control group of children not following a phosphate restriction was unfortunately not used for comparison in this study. The authors focused on the changes in serum PTH for each individual over time (of 1-3 years). They felt that this was acceptable, given that they had previously conducted a pilot study, which proved to be successful in controlling secondary hyperparathyroidism with mild phosphate restriction and high dose phosphate binders. It is disappointing however, that they were not able to quantify the benefit from intervention compared with a control group. They state that complicated dietary and drug regimes are seldom successful in patients with chronic illness, particularly in children. If the child had a liking for a food with a high phosphorus content, it was allowed in moderation and the dosage of phosphate binder was increased accordingly. Tamanaha and colleagues however, failed to comment upon the difficulties commonly encountered in adherence to medication regimens, particularly in relation to phosphate binders (Curtin et al, 1997). Adherence to phosphate binders appears to be one of the greatest problems for children within the study unit, particularly for adolescent children.

Adherence to oral iron supplementation is also problematical, associated with its poor taste and ability to cause gastrointestinal upsets such as bloating, constipation or diarrhoea and vomiting. Oral iron seems to be much less well tolerated by children (NKF-DOQI, 1997). Iron preparations tend to turn stools black and adherence can be improved by warning the children and families about this prior to them starting the medication. The added difficulty is that oral iron is best absorbed when ingested without food or other medications (Piraio-Biroli et al, 1958). This is rarely achievable in practice however, and one has to accept that there is greater likelihood of them taking the prescribed iron when consumed with other medications, which if twice a day tend to be taken in the morning and at bedtime. Studies do not appear to have been conducted

to determine the best pattern for maximising both the adherence to and absorption of iron.

A nutrition intervention programme 'Protein Wise' was designed by dietitians employed for the MDRD study, which was based on behavioural principles and techniques (Gillis et al, 1995). Behavioural approaches have been shown to support change in the short term, however, they usually fail to maintain change in the long term (Leventhal & Cameron, 1987). Leventhal and Cameron (1987) suggest that failure occurs when contact with an interventionist is less frequent or absent, when initial symptoms of illness lessen, or when relapse into a previous pattern of behaviour does not provoke any symptoms. The dietitian can foster three critical aspects of change; self-efficacy, self-control and self-evaluation, although the person must be willing to make a commitment and is ultimately responsible for modifying their eating behaviour (Baldwin & Falciglia, 1995). Active participation by the patient in setting goals is critical for success in program compliance (Mazzeo-Caputo et al, 1985). Taking small incremental steps toward a long-term goal provides a greater chance for success, increases self-efficacy and lessens vulnerability to lowered self-esteem. The major goal of the study was to support long-term adherence by developing self-management skills and increase feelings of self-efficacy.

Participants in the MDRD programme met individually with the dietitian once a month. During the baseline period, patients signed a contract of what would be expected of them and recorded in their own words, reasons for joining the study. The mean time a dietitian spent counselling a participant was 66 minutes/month during months 1-4, 49 minutes/month during months 5-12 and 39 minutes/month during months 13-36. Total time for all participant visits declined from 183 minutes per visit during months 1-4 to 116 minutes per visit during months 25-36 (Dolecek et al, 1995). Significantly more time was required for participants consuming the low-protein and very-low-protein diets than for those consuming the usual-protein diet (controls).

The 32 intervention strategies used by the dietitians in the MDRD study were grouped into four types: knowledge and skills, feedback, modelling and support. Adherence was measured by the agreement between estimated protein intake (Maroni et al, 1985) and dietary data (Milas et al, 1995). Adherence to low-protein eating patterns was found to

require social support and assistance for replacing energy lost by a decrease in protein intake. Participant's adherence to modified protein intakes was related to their rating of satisfaction with the diet (Coyne et al, 1995). The interventions used most often by dietitians during the study involved providing feedback based on self-monitoring and/or food records, reviewing adherence or biochemistry data, providing low protein foods and reviewing graphs of adherence progress. The components rated as 'very useful' by the largest percentage of participants were self-monitoring, and dietitian counselling and support. This was rated more highly by adherent patients than those found to be non-adherent (Milas et al, 1995). The role of the dietitian seemed to shift from one of instructor to one of provider of support and adherence feedback, and the role of the participant became increasingly one of taking responsibility for their own behavioural change process. It is imperative that dietitians record their intervention strategies. Factors associated with patient adherence and professional time required to deliver these interventions should be examined to determine cost-effectiveness in the provision of optimal dietetic care for children with renal disease.

There are few papers currently published relating to factors associated with dietary adherence and it is an area that many centres that deal with chronic diseases such as renal disease, diabetes and cystic fibrosis are starting to address. The literature review for this section is therefore rather limited, and predominantly focuses on the well-reported work done by dietitians involved in the MDRD study of adults. There is even less literature available in relation to children, where food choice changes with age, and hence subgroups of children across the age ranges are needed to assess compliance to and provide strategies for, the management of diet and medications.

There seems to be little debate around the strategies that need to be employed to improve adherence. The literature suggests that behavioural strategies including participant self-monitoring and provision of feedback by the dietitian are positively related to adherence (Wright, 1998; Milas et al, 1995; Gillis et al, 1995; Chan & Greene, 1994). Debate however exists in clinical practice, on being able to provide the resources that are necessary to support these strategies. Such resources involve increased dietetic time, obtaining appropriate markers of feedback such as accurate food intake records and biochemical markers such as urinary urea nitrogen excretion if

enforcing a protein restriction, and provision of social support (Sussmann, 2001; Dolecek et al, 1995; Milas et al, 1995).

Dietitians are specifically trained to provide dietary advice on an individual basis, accounting for socio-economic circumstances and learnt behaviour which have to be considered when attempting to modify eating behaviour. The concordance approach therefore tends to be part of the established role of the dietitian, negotiating changes that the child and family feel able to make and providing suggestions on how they might make them. Involving the child in the decision making process will facilitate behavioural change, which from clinical experience may even be successful in children as young as 4-5 years age. If dietary intervention is instigated early in the course of CRI, dietary alterations can be targeted in a step-wise, individualised manner, developing the child and family's self-confidence and motivation over a period of time.

1.4 Summary of current nutritional challenges in the management of children with CRI (Table 1.4)

Parameter and relevant section	Dietary considerations	Medical considerations
Progression of CRI Sections 1.3.1 - 1.3.4	Sodium - restrict (max. of 100mmol/d) Protein - reduce (small portion of HBV protein twice a day) Phosphate - restrict (max 1000 mg/d) Lipids - restrict saturates (max 10% total energy)	Antihypertensives Antiproteinuric agents e.g. ACE inhibitors Phosphate binders Statins
Hypertension Section 1.3.1 & 1.3.2	Restrict sodium (max. 100mmol/d) Avoid excessive weight gain Encourage exercise	Antihypertensives Avoid hypercalcaemia and hyperparathyroidism Avoid EPO-induced hypertension
Growth Section 1.3.5	Adequate energy (100% EAR - ↑ unsaturated fats) Adequate protein (100% RNI) but avoid excess	Oral supplements or tube feeding Base e.g. bicarbonate Antihypertensives Growth Hormone
Hyperlipidaemia Section 1.3.6	Lipids - restrict saturates. Replace saturates with mono/poly-unsaturates Carbohydrates – restrict sugars	Statins
Renal osteodystrophy Section 1.3.7	Restrict phosphate (max 1000 mg/d) Ensure adequate calcium (at least 100% RNI)	Phosphate binders (calcium based or calcium-free) Vitamin D analogue
Renal anaemia Section 1.3.8	Adequate micronutrient intake (RNI), especially iron, folate, and vitamins B_{12} & C. Avoid inhibitors of iron absorption	Ferrous salt (oral) or intravenous iron Erythropoietin (rhuEPO) Avoid hyperparathyroidism & chronic infection

1.5 Rationale for aims and structure of the study

This study hopes to provide a critical appraisal of the current provision of joint dietetic and medical care for children with CRI, through evaluation of the following four aims.

Aims

1. To compare the validity of using serum cystatin C opposed to plasma creatinine/ height for estimation of GFR in screening for mild CRI and to compare serial measurements between cystatin C and creatinine/ height.

2. To compare baseline growth, dietary intakes and biochemical indices between children with differing levels of renal function.

3. To describe over a two year period the progress of children with differing levels of severity of CRI, in relation to their growth, nutritional intakes and biochemical status, whilst in receipt of a joint medical and dietetic package of care.

4. To ascertain the level of adherence over the 2 year period to the advice given.

Rationale

Aim 1

To compare the validity of using serum cystatin C opposed to plasma creatinine/ height for estimation of GFR in screening for mild CRI. A study involving classification of children into groups depending on the severity of their renal disease followed by monitoring the progression of their disease over time, requires a reliable method of estimation of GFR. An established gold standard for measuring GFR (^{51}Cr-EDTA clearance) was used for classification of children into groups at recruitment. Frequent estimations of GFR using a radio-isotope or other method involving sequential blood tests and urinary collections are contra-indicated however, due to their invasive nature and inconvenience to the patient. Concerns have been raised over estimations of GFR using plasma or urinary creatinine concentrations, due to the fact that creatinine is not

only freely filtered by the glomerulus, but is also secreted by renal tubular cells and is affected by muscle mass and dietary intake (Chapter 4). As a result, research has focused on identifying other suitable indirect markers of GFR, such as the recently identified serum cystatin C. Identification of CRI at an early stage may be important, if medical and/ or dietetic interventions can be shown to be of benefit in delaying the progression of CRI and/ or treating symptoms in children with mild CRI. The first aim of the study was designed to assess whether cystatin C was a better marker of GFR than the currently used creatinine/ height estimation as a screening tool. Published reports are not yet available concerning the use of serum cystatin C as a marker of progression of CRI. This is the first study to obtain serial measurements of cystatin C alongside creatinine/ height for monitoring the progression of CRI, although unfortunately a final ^{51}Cr-EDTA measurement for comparison was not available, thereby limiting the conclusions that can be made from this data. It has however, been reported due to the absence of any other data in the literature on longitudinal cystatin C measurements at the current time, with the aim of highlighting areas that require further research.

Aim 2 and 3

I am one of two paediatric renal dietitians working for the Nottingham Children and Young People's Kidney Unit; one of 12 specialist supra-regional paediatric renal units within the UK, serving a total population of 5.5 million. A substantial proportion of time is spent reviewing nutritional status, biochemical parameters and growth in children on dialysis. All children referred with CRI for dietetic advice usually present with moderate to severe renal failure. It is rare for children with mild CRI to be considered for dietetic review. It is hoped that one of the major outcomes from this study would be to identify whether dietetic input should be requested for this group of children, and if so, what type of dietary advice would be appropriate. Aim 2 and 3 were identified to address this desired outcome.

Aim 2

Aim 2 was designed to establish whether there were differences in nutrition, growth and blood biochemistry between children with differing levels of renal function at baseline, for which a cross-sectional comparison between those with 'normal' renal function and

children with differing levels of severity of CRI was conducted. This aim, involving description of existing dietary intakes, should help to identify at what stage of CRI dietary factors may prove detrimental to growth and to nutritional and biochemical status. This will hopefully indicate whether children with milder forms of CRI should be referred to a paediatric renal dietitian in addition to those with more severe renal disease and if so, what advice should be given. Observations such as high phosphate intakes prior to elevated serum concentrations, high protein or high sodium intakes may often remain undetected in children with less severe renal failure. It is issues such as these that increasing evidence suggests may promote the progression of renal failure, if not limited early in the course of the disease.

Those children with more severe renal failure known to the specialist unit are likely to have had dietetic input prior to the study, and subsequently the degree of malnutrition and growth failure commonly reported in children with a GFR below 25% normal may be masked. Comparisons of baseline data between controls and three levels of CRI (mild, moderate and severe) however, may nevertheless highlight important differences, and may indicate the potential advantage of providing earlier dietetic and medical intervention. Earlier dietetic intervention may also be applicable to children with failing renal transplants, although this would require separate investigation and cannot be considered within the remit of this study.

Aim 3

The third aim is to describe over a two year period the individual progress of each child with varying levels of severity of CRI, with reference to nutrition, growth and biochemical variables, following joint medical and dietetic intervention. It is acknowledged that one cannot determine whether the package of care was successful in improving growth and blood biochemistry, and delaying progression of CRI, due to it being an observational rather than intervention study (section 7.1). It was not possible to have a control group for the longitudinal study, due to it being unethical to subject children to more frequent hospital visits and blood tests than is necessary. All children were eligible to receive the same package of care, depending on their clinical status, and intervention was not withheld for anyone if indicated. In addition, the advice given may have been different depending upon the clinical status of the child. If for example they

had polyuria or not, would determine whether they received a salt restriction, and if they were perhaps an older, overweight child with mild CRI, they may have been advised to reduce rather than increase their energy intake. Outcomes regarding growth, nutritional status and biochemical variables can be affected by many factors, including adjunct clinical and pharmacological therapy, which could not be controlled for. As a result, it is not possible to determine any cause or effect relationships between dietary intervention and nutritional/ biochemical status. Nevertheless, it is hoped that suggestions for further work and improvements in current clinical practice can be proposed, based on observed changes in nutrition, growth, blood biochemistry and estimated GFR within individuals, and between groups of children with CRI over time.

Foreman et al (1996) for the GFRD study identified the need to establish a better understanding of the dietary intake patterns of children with CRI, in order to make nutritional recommendations, and as a result, produced a comprehensive report on the nutrient intake of children with varying levels of CRI. Despite this, little conclusive information could be provided on appropriate recommendations and how they could be achieved in practice, as their study did not assess nutrient intervention. Recommendations for the nutritional management of the child with mild to moderate CRI were based on reports in the literature (Sedman et al, 1996), and like most other reports of such a nature (Hellerstein et al, 1987; Yang et al, 1988-89), provide recommendations on the level of intakes of specific nutrients, but do not attempt to translate them into a package of practical dietary care. One of the few papers offering some practical dietary guidelines was by Chan (1973), who presented a variety of prescriptive diets incorporating protein exchanges for infants and children with severe CRI. Such prescriptive diets however, tend not to be used today in the management of children with severe CRI.

There appear to have been few published reports directly assessing the impact of a 'package of care' of dietary interventions for children and their families with more severe CRI, let alone those with mild CRI. Most studies tend to focus on the impact of changing one nutrient on the course, or symptom of renal disease. Evaluation of dietary intervention is complex, as nutrition is just one of the factors involved in growth and influence on biochemical parameters. There are many conflicting reports on the relationship between a nutrient and clinical symptom, probably in part due to the

heterogeneity of the populations studied (associated with such factors as varying underlying diagnoses and age), and the small samples of children recruited due to the rarity of CRI in children. Frequently a number of nutrients require modification simultaneously, and often changing the intake of one nutrient will tend to have a 'knock-on effect' on the intake of other foods and nutrients. As patients consume foods, not separate nutrients, dietary manipulation should be evaluated as a whole package, focusing on the change to both foods and nutrients.

Aim 4

The European multicentre study assessing the effects of a protein restricted, adequate energy diet on the rate of progression, growth and development in children with CRI, included monitoring adherence to the diet with repeat food diaries every 4 months over a 2-3 year period. Whether this level of dietary counselling could be maintained in a clinical setting however, remains doubtful. Diet is part of everyday life, and hence relies on patient co-operation. As D'Amico and Gentile (1993) state, 'It is easier and more immediately satisfying (for physicians) to prescribe medications than to convince patients to change their dietary habits.....To achieve good results with diet, a dedicated and experienced staff is of fundamental importance'. Despite a majority of the dietary recommendations being applicable for as long as the child has CRI, there appears to be a lack of prospective data in children to evaluate long-term adherence to this advice in the clinical setting. The fourth and final aim of this study was therefore designed to establish to what extent the individual was able to adhere to the individualised package of dietary recommendations, via observing changes in foods that formed the greatest contributions to specific nutrients over a two year period.

Many of the nutritional recommendations suggested by authors, particularly with reference to low protein and phosphate diets are particularly restrictive, requiring a number of additional medications to compensate for reduction in specific nutrients. Whether this will prove to be warranted, in light of increasing research in favour of diet successfully delaying the progression of CRI remains to be seen. In the meantime, results from the final aim of this study should indicate the ability of children to follow somewhat less restricted nutritional advice, and provide an insight into successful versus unsuccessful nutritional practice.

The overall contribution of dietary interventions in the every day practice of a specialist paediatric renal unit requires evaluation. It is hoped that the results of this study will provide an insight into areas of dietary and medical interventions that require further exploration, before the development of evidence based clinical guidelines for the management of children at differing stages of renal failure can occur. These guidelines should also refer to how these recommendations can be achieved in practice, whilst minimising the consequent adverse effects on the quality of life for the child and family.

Structure

Volume I represents the main body of the thesis, and contains all 7 chapters, with tables and figures of summaries of results and ending with the bibliography. Volume II contains all the appendices. The first three appendices relate to chapters 4, 5 and 6 respectively, and provide the majority of the individual data relating to growth, nutrition and biochemical variables. The fourth and final appendix contains the dietary information that is given to children and their families on an individual basis.

In volume one, chapter two concerns a review of the methods of assessment of nutritional status that are currently available, and considers those pertaining to dietary survey methods, anthropometry and biochemical variables.

Chapter three relates to patients and methods, and includes the demography of the children recruited to, and the methods used for, the study. The methods pertain to those of nutritional assessment, which are subdivided into those concerning dietary assessment, anthropometry and blood pressure, and biochemical markers. Current practical dietary advice given during the study is also outlined and the information sheets given to children and families can be found in appendix 4. The methodology is relevant to the second, third and fourth aim of the study. A summary of the study protocol and the statistics used in the study are also provided.

The fourth chapter, related to the first aim of the study is dedicated to the estimation of GFR; the marker of level of kidney function, and includes the literature review,

methodology, results and discussion. Data on the change in renal function forms appendix 1. Chapter five provides baseline results, the majority of which are tabled in appendix 2. Comparisons are drawn between the four groups; mild, moderate and severe CRI and those with 'normal' renal function, thereby addressing the second aim of the study. Children deemed to have 'normal' renal function provided baseline data only and were not included in the two year follow-up. The results are considered in sections i.e. those concerning anthropometry and blood pressure, nutrient intake and biochemical parameters. A paper has been published on a subset of this data (Norman et al, 2000).

The results from the two year follow-up are presented in the sixth chapter, commencing with descriptions about the patients who remained within the study or the reasons for not completing the study. The longitudinal results are dealt with in a similar manner to those presented in chapter five, but concentrate on changes for each individual in variables over time (tabled data in appendix 3). The order of appearance of sections within this chapter is different however, and arranged so that comparison can occur between variables that may exhibit an association. This commences with what is considered to be the most important clinical outcome in children, i.e. that of growth, along with the marker of overall nutrient intake; that of energy, so that growth, energy and protein intakes are considered first. The need for inclusion of tables of individual data meant that certain nutrients had to be grouped together within sections, which was appropriate for all variables other than sodium, which had to be considered along with calcium and phosphate. The final section of chapter six considers changes made in actual food intake over the two year period for the cohort as a whole, answers to which address the final aim of the study.

Chapter seven concerns discussion of results and highlights the limitations associated with the study and methods. The discussion draws upon both the results related to anthropometry and blood pressure, nutrient intake and concordance to dietary advice, progression of CRI, and blood biochemistry at baseline, and the subsequent changes in the same variables over the two year period. The chapter is set out so that the variables are discussed in relation to the different conditions associated with renal disease, such as progression of CRI, growth, bone disease and anaemia, as set out and described in chapter 1. Conclusions and recommendations for future clinical practice and further

work are summarised in the final chapter. I hope you enjoy your read and find this thesis as stimulating and thought-provoking as I have. Perhaps it will leave you considering embracing some of the recommendations made for further research.

Chapter Two

ASSESSMENT OF NUTRITIONAL STATUS

There is no single measure or 'gold standard' to assess and define optimal nutritional status for children with CRI, and practical clinical nutritional assessment methods with a high degree of sensitivity are not yet available (Potter et al, 1978). A combination of methods is therefore employed in clinical practice to obtain an overall clinical impression. Assessment of growth and body composition, visceral protein status and dietary intake helps to determine nutritional status. Bilbrey and Cohen (1989) found a relationship between mortality in adult haemodialysis patients and a protein-energy malnutrition index, using a scoring system with eight variables, including anthropometric, biochemical (albumin and transferrin), total lymphocyte counts and clinical evaluation.

Reported dietary intakes can help contribute to determination of nutritional status if one can be confident that they are a true representation of actual food intake (section 2.1). Growth is one of the most important clinical outcomes in the management of children and is a sensitive but non-specific marker of nutritional status in children (Hellerstein et al, 1987). Weight and height measurements therefore play a significant part in the anthropometrical assessment of children (section 2.2). Biochemical markers are used to assess nutritional status and provide clinical information concerning the management of conditions such as renal osteodystrophy and renal anaemia (section 2.3).

Assessing nutritional status in children may be required more frequently than for adults because of changing needs for growth and development. The reduction in energy and certain other nutrients noted in various studies (section 1.3.5), emphasises the importance of careful nutritional assessment and the need for early supplementation. Ongoing nutritional assessment with particular reference to energy intake, weight change and statural growth is essential for good management in children (Hellerstein et al, 1987).

2.1 Dietary Survey Methods

The usual aim of any dietary survey is to discover the habitual intake of individuals. 'Habitual intake' is a theoretical concept representing a dietary intake, which averaged over a prolonged period, would maintain body weight in an adult (Black et al, 2000), and produce increases in weight and height in accordance with that expected for age in children. There are several methods currently available for determining habitual intake: precise weighing method, weighed inventory, diet diary, diet history ('usual' intake), diet recall (actual intake) and frequency questionnaires (Fehily, 1983). Factors to be considered in the selection of an appropriate method for estimating dietary intake consist of the purpose of the study, population or group studied, precision of measurement required, costs, and length of time to be covered (Fehily, 1983). Usually, the more accurate the method, the greater the degree of subject co-operation required and the lower the response rate. Hence, when selecting a method, a compromise may have to be reached.

The **precise weighing** method involves weighing all the ingredients used in the preparation of dishes, the inedible wastage, the cooked weight of the individual's portion and the plate waste. Unlike the other methods that use food tables, nutrient intakes can be determined by chemical analysis of aliquot samples. The method requires a great deal of subject co-operation and is therefore difficult to apply to a representative sample of the population. It also requires a significant amount of supervision, which may interfere with the family dynamics and result in a non-representative eating pattern.

In the **weighed inventory** method, the food is weighed and recorded immediately before consumption and plate waste is also weighed. Subjects are provided with a log-book and a set of balance or electronic scales. Nutrient intakes can be calculated with the aid of food composition tables. A disadvantage is in assessing meals eaten away from home. For these, a description of the foods with an estimate of portion sizes using household measures is usually accepted, or the foods can be photographed and subsequently compared to standard slides, as described by Elwood and Bird (1983). There is a tendency to under-record in association with the additional effort required by the individual (Schoeller, 1990). The method requires approximately three visits to the home to ensure the inventory is completed satisfactorily and hence is often not practical

with limited resources. The response rates for the weighed inventory method tends to be lower than that of other less demanding methods such as the questionnaire (Fehily, 1983). Higher response rates are more easily obtained if subjects feel that the study will be of benefit to them or their peers.

The **diet diary (semi-quantitative)** method involves documenting estimations of weights of all food and drink consumed in a booklet, using portion sizes obtained from household measures e.g. spoons, cups or weights from packets and tins (Nelson & Nettleton, 1980). Other foods would be classed as small, medium or large portions or the dimensions described. The subject's ability to estimate portion sizes however does vary. The information is subsequently converted to weights via standardised food portion sizes and compared to food composition tables, usually with the aid of a computer dietary package. Inconsistencies are evident between standard food tables, attributed to different methods of chemical analysis, sampling procedures or factors used to convert analysed values to nutrients (Bingham, 1987). Random errors are introduced as values are based on analytical averages of representative food samples. Increasing the number of observations reduces this source of error. In the UK, McCance and Widdowson food tables (Holland et al, 1991) are the most commonly used in clinical practice.

The **diet history** was developed as a research tool by Burke in 1947. The diet history is an interview method which aims to discover the usual food intake pattern of individuals over a relatively long period of time. Foods are recorded as usual portions in household measures, including frequency over a given period, noting the common variations in food items. The diet history technique however is difficult to standardise, and is open to observer bias (Black et al, 1993). Further disadvantages include the fact that the interviewer should be a dietitian/nutritionist trained in obtaining diet histories, where the importance of avoiding leading questions and suggesting answers is paramount. The mood or mental energy of the interviewer or interviewee, or the circumstances of the interview can also affect the results and the interview usually takes a minimum of an hour, where loss of concentration is likely to occur. The interview technique however, can be used to establish other relevant information such as the presence or absence of nausea, vomiting, diarrhoea and constipation, activity level and socio-economic status.

Dietary recall requires subjects to recall all food and drink consumed over a specified period, usually 24 hours, estimating portion sizes, often with the aid of photographs and food models which have been shown to reduce the variance in estimates (Rutishauser, 1982). There is a risk with the use of these aids in inducing a 'direct response', unless a number of sizes of the same food model or photograph are available, which would result in the need for a large number of models. Graduated food models were developed to represent a portion e.g. mound, slice etc (Moore et al, 1967) and despite their wide use in dietary surveys, there appears to be few studies to validate this tool. Advantages are that the respondents may not have the opportunity to modify their usual food behaviour in anticipation of a dietary evaluation and they do not have to be literate. The disadvantage with the 24-hour recall is that it relies on memory, making it unsuitable in particular for children and the elderly. There is a tendency to underestimate food portions, although those who eat small quantities are more likely to over-report their intake (Bandini et al, 1990).

The use of **food frequency methods and questionnaires** has several advantages in that data can be collected quickly and cheaply, with no observer bias. However, with any postal method, answers may be incomplete or ambiguous. The record is not designed for quantitative analysis but should permit grading of food items into 4 or 5 categories so that extremes can be identified and tested for in association with disease. A carefully designed questionnaire is therefore important. 'Recall' methods have been shown to reduce the risk of sampling bias, with an average response rate to 'recall' methods of 77% compared to 68% with weighed methods (Nelson and Nettleton, 1980).

Bingham (1987) lists nine sources of error in methods used to assess dietary intake, such as coding errors and change in diet. Errors for estimation of a nutrient intake of $\pm$ 10% is often referred to as being acceptable. It is important to note that the population differences in intake may not exceed 10%, in which case the error involved would be greater than the difference under investigation. Validation is the demonstration that a method measures what it is intended to measure, and requires that the truth be known (Johansson et al, 1992). True validation could not be obtained with any of the methods until the 1980's, as true usual intake could not be determined. 'Relative' validation i.e. the validation of one method against another was used to determine the ability of a dietary assessment method to represent 'true' intake, with the precise weighing method

being regarded as the 'gold standard'. Several independent biological markers of dietary intake however, have since been developed, against which the chosen dietary survey method can be validated. Prentice and colleagues (1986) used the doubly labelled water technique to validate dietary assessment of energy intake, Isaksson (1980) proposed the use of 24-hour urinary nitrogen excretion to validate protein intake, and Schachter et al (1980) observed the close association between urinary and dietary sodium intakes. Urinary nitrogen excretion is relatively simple at the laboratory level but is not acceptable as a routine field technique. Conversely, the doubly labelled water method is an ideal field technique, but is very expensive and requires sophisticated laboratory support (Black et al, 1993).

A fundamental principle of energy physiology is that if body weight and composition are stable, total energy expenditure (TEE) and energy intake (EI) must be equal (Goldberg et al, 1991). A random selection of a group of individuals would be expected to have a stable weight, although weights for individuals may vary. The doubly labelled water technique measures energy expenditure in free-living individuals over periods ranging from 5 days in infants to about 14 days or longer in adults (IDECG, 1990). The subject drinks water enriched with the naturally occurring stable isotopes of deuterium ($^2H_2$) and ^{18}O. These disperse throughout the body water, enter the metabolic pool, and are gradually lost from the body. The level of isotope in the body is measured using mass spectrometry, in a small sample of urine collected each day for 5-28 days, depending on the study design. The disappearance rates of deuterium and ^{18}O measure the turnover of water and water plus carbon dioxide respectively. Carbon dioxide production is calculated by the difference between these measures and is used in indirect calorimetric equations to give calculated energy expenditure.

Energy requirements vary with age, sex and body size, as does basal metabolic rate (BMR). Absolute energy requirements (TEE) can be expressed as multiples of BMR (FAO/WHO/UNU, 1985), denoted by the ratio TEE:BMR, the value for which is known as the physical activity level (PAL). The 1985 FAO/WHO/UNU report calculated that a PAL of 1.27 (i.e. TEE = 1.27 x BMR) is the minimum for survival, which is not compatible with long term health and does not make allowance for the energy needed to earn a living or prepare food. Using factorial calculations, the report stated that for a sedentary lifestyle, the estimated average PAL would be 1.55.

Schofield (1985) demonstrated that BMR is highly correlated with body weight, with coefficients of variation of approximately 8% when predicting an individual BMR from equations derived from body weight.

The mean reported energy intake (EI) in any study can be expressed as a multiple of BMR estimated from the Schofield (1985) equations (EI:BMR), and compared with the expected PAL for that population (Goldberg et al, 1991). Goldberg and colleagues (1991) determined confidence limits (cut-offs) for agreement between EI:BMR and PAL, and produced minimum cut-off limits for energy intake below which a person of a given sex, age and body weight could not live a normal life-style. This data was produced from analysis on adult men and women in affluent societies with sedentary lifestyles and did not include a subset of children. The cut-offs vary depending upon the number of days of dietary assessment and the sample size, with the sample size exerting a much larger effect. For 10 subjects, cut-off 2 for the lower 95% confidence limit is stated to be 1.39 x BMR for a 4 day dietary assessment, whereas for one individual, it would be as low as 1.1 x BMR. The Goldberg cut-off 2 can be used to test whether reported energy intakes are a plausible measure of the food consumed during the measurement period. Results falling below the cut-off limits should be recognised as being incompatible with long-term maintenance of energy balance and therefore long-term survival. Such results would suggest either under-eating, under-recording or a combination of both during the recording period (Goris et al, 2001).

The Goldberg cut-offs have a number of additional limitations, including poor sensitivity for defining invalid reports at the individual level, wide confidence limits so that only extreme degrees of miss-reporting can be identified and no distinction can be made between the varying degrees of miss-reporting (Black, 2000a). There is increasing concern that a PAL of 1.55 is too conservative for normally active populations, and a blanket cut-off of 1.55 can only identify about 50% of those defined as under-reporters by the TEE:EI ratio (Black, 2000b). The cut-off also ignores those who may have under-reported from high energy requirements, but whose reported intake had not fallen below this conservative cut-off. Black (2000a) recommends that dietary studies should include an internal validation procedure using a biological marker such as energy expenditure or urinary nitrogen excretion to assess the degree of under-reporting, weight and height should be recorded to elicit under-eating, and information

should be obtained about the physical activity or lifestyle of the population to ascertain an appropriate PAL value for comparison.

The Schofield equations for estimating BMR in children under 10 years of age are based on small data sets. As a result, the Department of Health recommendations for energy intakes in children less than 10 years were based on reported energy intakes, rather than energy expenditure calculated from BMR, as used for other population groups (DoH, 1991). The combination of limited data in children for estimating BMR and the fact the derived PAL cut-offs did not include children, brings to question whether the method described by Goldberg and colleagues (1991) should be used for assessing the adequacy of reported energy intakes in this population. Unfortunately, the recent report by Black (2000a) did not explore the use of appropriate Goldberg cut-off values for children. Evaluation of energy requirements in children by Torun et al (1996) concluded that Schofield calculations of BMR tend to overestimate results, although there was an absence of data relating to Caucasian children under 7 years of age. Henry et al (1999) on behalf of the International Dietary Energy Consultancy Group (IDECG) attempted to produce new equations to estimate BMR in children aged 10-15 years, incorporating assessments of pubertal stage, but found that this afforded only minor improvements in the estimation of BMR from linear regression equations. New values for PAL for different age groups of children have been proposed in the review by Torun et al (1996) until appropriate 'cut-off' values, based on fundamental principles of energy physiology are derived for acceptable reported energy intakes in children. They recommend using the following provisional minimum and maximum PAL cut-off points: 1-5 years (boys and girls): 1.28-1.79 x BMR; 6-18 years: 1.39-2.24 x BMR (boys) and 1.3 – 2.1 x BMR (girls). In addition, the use of Goldberg cut-offs has not been validated in subjects with chronic diseases such as CRI. As energy requirements for children with CRI are thought to be similar to the normal healthy population (Hellerstein et al, 1987), it would be expected that the BMR would also be equivalent, and thus use of this method in CRI should not be contraindicated.

The urinary nitrogen excretion method to validate protein intake involves collecting urine in containers with boric acid as a preservative for 24-hour periods. A second 24-hour urine collection is usually made 2-4 days later. Completeness of the urine collection is verified by PABACHEK (Bingham & Cummings, 1983). This involves

taking 3 capsules containing 80 mg p-amino benzoic acid (PABA), one on rising and one with the midday and evening meal. Urine collections containing less than 205 mg (85% of the dose) are rejected as incomplete. The PABACHEK test however, cannot detect over-collection and people sometimes refuse or forget to take the PABA capsules (Johansson et al, 1992). Creatinine excretion has been used to check completeness of 24 hour urine samples (Bingham, 1987). Creatinine excretion however, is influenced by the meat content of the diet and therefore any prospective study which may affect the dietary intake of meat would prohibit the use of this method to check completeness of urine sampling (Johansson et al, 1992). Total urinary nitrogen is determined by the Kjeldahl method (measurement made on a Technicon Autoanalyser with histidine as a quality control).

For subjects in nitrogen balance, urine nitrogen reflects nitrogen intake. To validate methods of dietary assessment using the 24 hour urine nitrogen technique, the average urinary nitrogen (UN) can be compared to the average nitrogen intake (NI), as a ratio UN: NI. A higher than expected UN:NI value reflects either incomplete reporting of NI (protein intake), or a reduced intake leading to oxidisation of protein to supply energy. Bingham & Cummings (1985) found extra-renal losses to be proportional to total nitrogen turnover and the average UN:NI value to be 0.81 (SD 0.05). Subjects with a UN:NI value greater than 1.0 have been suggested to be under-reporters (Black et al, 2000). Alternatively, protein intake can be calculated as (UN + 2) x 6.25g, assuming that extra-renal losses of N are constant at 2 g/d in adults (Isaksson, 1980). This calculated protein intake can be compared directly to the reported protein intake, and a value of 1.0 would be expected. This may not be the case in children however, where accumulation of nitrogen will occur, associated with growth. The use of this tool for validation of reported protein intakes in children has not yet been evaluated. This tool is unlikely to be valid in patients with substantial proteinuria, where urinary nitrogen could be much greater than nitrogen intake, and in patients with CRI where excretion of nitrogen is incomplete.

Nitrogen intake can be estimated using a biological marker in patients with CRI, via measurement of urea nitrogen appearance (UNA) (Maroni et al, 1985). Nitrogen balance (NB) in CRI is determined by the difference between dietary NI (estimated from dietary records), UNA and any urinary protein nitrogen losses (UprV /6.25), where

V is the volume of distribution of urea (Abitbol et al, 1996). Urea nitrogen appearance was calculated in children with CRI from the 24-hour interval accumulation of total blood urea nitrogen (BUN) and 24-hour excretion of urinary urea nitrogen (UUN) (Abitbol & Holliday, 1978). The volume of distribution of urea can be estimated as for that of water, which averages 60% of body weight in adult CRI patients. The assumption was made that the distribution of water was similar for children.

The equations are as follows:

$$UNA\ (gN/d) = [(BUN_{Time\ 24} - BUN_{Time\ 0}) \times 0.6 \times \text{Body weight (kg)}] + UUN\ (g)$$

$$NB\ (gN/d) = NI - UNA - UprV/6.25.$$

During steady state conditions, nitrogen intake is equal to or slightly greater than nitrogen losses, the latter being referred to as total nitrogen appearance (TNA). TNA is the sum of dialysate, urine and faecal nitrogen losses, plus the change in body urea-nitrogen content. Since the nitrogen content of protein is relatively constant at 16%, the protein equivalent of total nitrogen appearance (PNA) can be estimated by multiplying TNA by 6.25. In stable patients, the nitrogen output in faeces, skin and hair is constant and ignored to simplify the calculation. In the clinically stable patient, TNA is strongly correlated with UNA, and thus PNA derived from UNA in a 24 hour sample is a valid estimate of protein intake (Maroni et al, 1985). Little variation was observed in the mean values of the components of non-urea nitrogen with differing protein intakes, with an average non-urea urinary nitrogen (NUN) of 31 mg N/kg/d. The following formula was thus devised (Maroni et al, 1985):

$$NI\ (g/d) = UNA + [0.031\ g\ N \times \text{body weight (kg)}].$$

Since protein requirements are determined primarily by fat-free, oedema-free body mass, PNA is typically normalised (nPNA) to a function of body weight i.e. per kg body weight, using estimated dry weight rather than actual body weight.

The assessment of nitrogen use and requirements for growth in infants and children is complicated by the fact that a positive nitrogen balance would be expected if growth is to occur, and thus PNA will underestimate actual protein intake. It is estimated that 7-10 mg/ kg/ d of protein is required for growth (FAO/ WHO/ UNU, 1985). Wingen et al (1993) state that in children with normal growth, the difference between NI and UNA should be at least 0.041 g/ kg/ d (0.031 NUN + 0.1 growth). If it is much less than this, it is suggestive of under-reporting. Wingen and colleagues (1993) suggest that the

equations derived by Maroni et al (1985) for adults are also suitable for children, as long as their protein intake approximates 1g/ kg/ d. The equations however, seem to underestimate protein intake in the very young children who have much higher protein intakes. The alternative equation proposed by Wingen et al (1993) is:

Protein intake (g/ kg/ d) = UNA (g/ kg/ d) x 9.5.

Orejas et al, (1996) compared the use of 3 day weighed dietary records with 24 hour urinary nitrogen excretion to assess protein intake in children with CRI. Daily nitrogen intake was 11.05 g by dietary record and 8.52 g by urea excretion with a significant correlation between the two ($r=0.61$; $p=0.0003$), although the difference between the two was 2.5 g, which was greater than the mean estimated nitrogen intake calculated from the methods combined. The differences observed in the various studies can, in part, be ascribed to the great variability of protein intake in humans (Stuff et al, 1983) and the relatively slow adaptation of nitrogen urinary excretion to dietary changes (4-7 day delay). Orejas and colleagues (1996) conclude that although measurement of urinary nitrogen excretion in a 24-hour sample is a useful method for validating protein intake in a group of children with CRI, it should not be used as a replacement for dietary records. The collection of 24 hour urine samples is very laborious for the child and family, with inherent difficulties in ensuring that the 24 hour collections are complete. For this reason, they are rarely conducted in routine clinical practice in the study unit, and assessment of protein intake was thus solely based on yearly 3 day dietary records during the study.

Assessment of dietary sodium intake from food diaries is notoriously unreliable, due to difficulties in quantifying added salt to food, and the large variation in sodium content of manufactured and home-made dishes. Urinary sodium excretion is the major source of sodium loss. Faecal sodium is usually less than 4 mmol/d and losses through the skin are small (Blumenkrantz et al, 1980). Urinary sodium excretion has been shown to be a good measure of short-term sodium intake, with an average urinary sodium excretion corresponding to 86% of total sodium intake in adults (Holbrook et al, 1984). Schachter et al (1980) however, found only an average 5% difference between sodium intake assessed from unweighed duplicate portions and excretion of sodium from 24 hour urine collections, which would suggest that correction for unmeasured sodium losses is not necessary for extrapolation to sodium intake. As previously mentioned, 24 hour urinary

collections are not routinely carried out in the study unit, due to practical difficulties, and hence were unfortunately not available to compare with the estimated sodium intake from dietary diary analysis.

Ideally, all studies should incorporate independent measures of validity and determination as to whether substantial bias is present. Where bias is found, it should be less than 5% (IDECG, 1990). The presence of bias may not be important if it operates equally across all members of a population, so that internal comparisons remain valid (Black et al, 1991). It may also not be important if subjects are studied more than once and act as their own controls, although in a longitudinal study involving dietary intervention, the response may alter and thus affect the degree of bias. Bias becomes important if absolute levels of intake are to be measured, and the presence or absence of deficient intakes is to be determined. False conclusions can be drawn if bias is linked to a parameter of interest, or if attempting to establish a mean population intake. Bias on measurement of energy is likely to lead to bias on measurement of other nutrients closely correlated, such as fat, carbohydrate and B vitamins (Black et al, 1991).

It has been suggested that individuals with high energy intakes tend to underestimate their intake, whereas those with low intakes tend to overestimate intake (Bandini et al, 1990). Black et al (1991) evaluated the validity of reported energy intakes in 37 published dietary studies of adults and concluded that self-reported dietary intake is frequently biased towards underestimation of habitual energy intake. Livingstone et al (1990) found a high level of repeatability in measurements made a year apart, indicating that the bias identified in many of the subjects was reproducible over long intervals i.e. individuals are consistently 'good' or 'poor' reporters of food intake. Subject-specific bias to dietary assessment has been confirmed in a recent review by Black & Cole (2001), with a mean bias to under-reporting among this group of 20%, irrespective of the dietary assessment tool used. Several large dietary surveys have found that a high body mass index is associated with a greater probability of low reported energy intake (Prentice et al, 1986; Livingstone et al, 1990). Preoccupation with body weight and image, which may lead to real or apparent dietary restraint, seems to be well developed in girls with normal and low weight by the age of 12 years. Similar, although less marked trends have been observed in adolescent boys (Livingstone et al, 1992). Age

has also been suggested to be a variable affecting response to dietary assessment from children, where weighed records gave unbiased results in 3-5 and 7-9 year olds, but an excess of discrepancies between reported energy intakes and energy expenditure were noted in 12 year olds (-11%) and 15-18 year olds (-24%) (Black et al, 1993). This could be due to the fact that in young children overall control of food intake and responsibility for dietary reporting are shared by parents and other adults concerned with child caring. Younger children also have less unsupervised access to food in and out of home. Conversely, by early adolescence, the responsibility for reporting shifts more to the subjects themselves. Consequently, their greater food requirements in combination with unstructured eating patterns and a significant degree of eating outside the home, suggest that under-reporting may be partly due to forgetfulness and partly lack of compliance with a demanding protocol (Torun et al, 1996).

Though one person may differ markedly from another in their pattern and level of food consumption ('between-person' variation), each individual is also liable to vary considerably from day to day ('within-person' variation). This daily variation is more important for some nutrients than others. Bingham (1987) has tabled within-person coefficients of variation from a number of studies and notes that the extent of within-person variation in nutrient intake is greater for minerals, vitamins, cholesterol and foods, than energy or energy-yielding nutrients, partly due to the infrequency with which foods are eaten. The variation is usually 20-30% for energy, 20-40% for fat, 30-50% for calcium, iron, thiamin and dietary fibre, and as much as 40-70% for riboflavin, vitamin C, cholesterol and polyunsaturated fat. The extent of this daily variation differs significantly from one individual to another. Precision can be improved by increasing the number of observations on each individual (Sempos et al, 1991). Nelson et al (1989) however, found that 7 day weighed dietary records did not rank individuals with the degree of accuracy commonly assumed, although the degree of accuracy varied considerably with the age of the population being studied. Children under 4 years of age were adequately classified for a majority of nutrients, whereas for most minerals and vitamins for boys aged 5-17 yrs, and virtually all nutrients for girls aged 5-17 yrs, the dietary record appeared to be insufficient for ranking at a level at which $r = 0.9$.

The daily variation can be determined by observing the degree of misclassification between high and low consumers for individual nutrients on a daily basis, compared

with their averaged intake over a one week period (Marr & Heady, 1986). If one is prepared to accept 70% correct classification as being sufficiently reliable (with the consequence that approximately 4% individuals will be grossly misclassified), a survey of 3-4 days will be enough for most of the macronutrients (Marr & Heady, 1986). Records kept for much more than 3 days increase the likelihood of inaccurate reporting. It is generally agreed that periods of three or four days should include at least one weekend day because nutrient intakes of weekend days may differ greatly from those of weekdays (Fehily, 1983; Medlin & Skinner, 1988). For vitamins, minerals and fibre it is suggested that a record of at least 14 days is obtained which could be reasonably substituted by 4 records each of 4 days duration to improve compliance (Bingham, 1987). The weighed record is suggested to be more accurate than the semi-weighed record but requires more resources (Bingham, 1987). Questionnaires may be adequate to estimate intakes of certain nutrients such as dietary fibre and vitamin C, which are present in only a few foods of any significant quantity. A 24 hour period has been shown to be of very limited value in identifying intakes of individuals, even at the extremes of distribution, as it systematically underestimates food intake and fails to take account of daily variations in dietary habits (Marr, 1971).

Dietary surveys are prone to errors of reproducibility as a result of both inherent variations such as seasonal variation, periods of dieting to lose weight and intra/inter-observer variation. Inter-observer variation can be minimised by only using one observer. The use of computer programmes for calculating nutrient intakes with recommended standard portion sizes may help towards standardising the results obtained from two observers. Seasonal variation can be limited by carrying out all measurements at the same time of year or ensuring that the sub-sample studied in one season is comparable to those studied in other seasons. Reproducibility studies of dietary survey methods are difficult to interpret as the intake may remain stable or change, and dissimilar results on two occasions could either reflect an unreliable method or a reliable method measuring a change. Goris et al (2001) explored the degree of under-reporting that occurred during a 12 week exercise intervention study, and under-reporting was divided into under-eating and under-recording. Under-recording was measured by comparison of reported energy intake with energy expenditure as calculated from measured BMR and physical activity, which was determined using a tri-axial accelerometer for movement registration (Bouten et al, 1996). Under-eating was

calculated from the change in body weight over the recording week in comparison to stated energy intake. They observed that during the second period, the subjects ate less, and it has previously been suggested that repeated food recording can be seen to be a burden, which might result in subjects eating less (Westerterp et al, 1991). Johansson et al (1992) also observed a decreased ratio of energy intake to body weight that could not be explained by lower energy expenditure in a dietary intervention study. Johansson and colleagues (1992) showed a reduction in the ratio of dietary intakes to biological markers 6 and 12 months into the study, demonstrating that it is difficult to obtain valid dietary data one year after a dietary change, and suggested decreased compliance to the new dietary regimen.

Without validation of dietary intake data against biological markers, it is not possible to accurately conclude whether changes in dietary intake during an intervention study are due to miss-reporting or actual change in dietary habits. This is a major pitfall in the current study, but unfortunately 24 hour urine collections are not practical for many children, and although attempts are made to estimate the degree of miss-reporting of energy intakes in this study, the data for evaluation of energy expenditure in children is limited (Torun et al, 1996). Estimates of the ratio of energy intake to body weight to establish the degree of under-eating opposed to under-recording in children would not be valid, due to expected increases in weight associated with growth, which could potentially mask moderate under-eating. The use of body mass index instead would also be too complex, as a reduction in BMI does not distinguish between whether it is a relative loss in weight or gain in height.

The most useful clinical method for monitoring intake has been reported to be the 3-4 day weighed prospective dietary diary (Hellerstein et al, 1987). Chantler & Holliday (1987) showed a good correlation between 3-day prospective dietary records and double-bag analysis of all food consumed. Sodium and potassium intakes were calculated using semi-quantitative 3 day dietary diaries in thirty-five 3-5 year old children (Allison & Walker, 1986). For the children as a group, daily sodium intake calculated from the diaries was similar to that estimated more reliably from sodium excretion (Schachter et al, 1980). Wingen et al, (1993), on behalf of the European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood, chose a minimum of two 4-day weighed food diaries, inclusive of a weekend, to be completed

during the 6 month run-in period. Protein intake was also calculated from 24 h urinary urea-nitrogen excretion (Maroni et al, 1985). A close correlation between dietary diaries and urinary urea-nitrogen excretion ($r=0.88$; $p=0.0001$) was reported, although patients in the diet group were noted to under-report their protein intake whereas controls did not. Frequent evaluation of dietary intake is mandatory to prevent malnutrition and assess patient concordance, and constant follow-up should not be neglected (see section 1.3.9). Toigo and colleagues (1990) recommend a combination of dietary interviews and diaries written by the patients and discussed afterwards with the dietitian for giving the best information during routine dietary follow-up. They suggest that a diary is a valuable tool in teaching nutritional goals to patients and in improving concordance.

2.2 Anthropometry

Anthropometric assessment is a rapid, inexpensive and non-invasive means of determining short and long-term nutritional status. Clinical examination was demonstrated to be inaccurate in determining nutritional status, whereas anthropometry was deemed to be crucial (Cross et al, 1995). Numerous anthropometric measures are used in nutritional assessment, because no single measure can fully characterise nutritional status (Dwyer, 1991). Growth is a useful, sensitive but non-specific marker of nutritional status in children. Reliable assessment of growth requires the use of appropriate and consistent measuring techniques and good equipment (Hellerstein et al, 1987). All of the anthropometric measurements are more valid if measured serially.

Weight should be measured frequently. Infants should be measured without nappies to the nearest 0.01 kg and older children should be measured to the nearest 0.1 kg, wearing little or no outer clothing and no shoes. Weight measurements should ideally be taken at the same time of day after the bladder has been emptied, so that children in the same physiological state are compared (Zemel et al, 1997). A decrease in relative body weight (child's weight/ weight of normal child of same age, height and sex) may be one of the first indicators of malnutrition, usually preceding a loss of linear growth.

Head circumference is another important aspect of nutritional assessment in young children and should be measured for the first 1-2 years of life. A firm, non-stretchable measuring tape should be placed just above the eyebrows (supra-orbital ridges) and

around the occipital prominence at the back of the head, so that measurement is of the maximum head circumference. The tape should be pulled tightly enough to compress the hairs and the measurement recorded to the nearest 0.1cm.

The length of children under 18 months to 2 years of age should be obtained using an infantometer. This is a measurement table with a fixed headboard and moveable footboard positioned perpendicular to the table surface to measure crown-heel length in the supine position. Once the child is able to stand without assistance, standing height is measured. A difference of up to 2.5cm may be obtained on transition to the upright position. Standing height is best measured with a precise wall scale and right angle head indicator such as the Harpenden stadiometer. Ideally the same observer should be used but a number of staff, if trained by an auxologist, is acceptable. The measurement error for height is sufficiently large (approximately 0.5 cm) that an interval of at least six months is recommended to be assured of measurable growth in children and adolescents (Zemel et al, 1997).

Comparisons of height, weight and head circumference should be made using an appropriate growth chart (Hellerstein et al, 1987). One-time measurements reflect size, whilst serial measurements are necessary to determine growth. The goal is for the child's weight percentile to correspond to their height and head percentile, and to follow the same percentile curve over time. Low weight for height, low height for chronological age or a low head circumference in proportion to height may reflect chronic nutritional deficits. Both parental heights should be measured and recorded where possible in order to calculate mid-parental height; an aid to predicting final expected height of child. The calculation for boys is to obtain the average of both parents heights after adding 13cm to father's height. For girls, 13 cm is subtracted from the father's height before averaging (MacGillivray, 1993).

Until recently there was only one set of growth data, longitudinal in nature to refer to (Tanner et al, 1966), the charts produced by Castlemead, who also supply a growth programme useful for research purposes. The centile distributions are 3rd, 10th, 25th, 50th, 75th, 90th and 97th. The British growth standards have recently been updated based on cross sectional data (Freeman et al, 1995), and charts produced by the Child Growth Foundation have been incorporated into the parent-held Child Health Records. These

charts have different centile ranges, with nine curves at 0.4, 2, 9, 25, 50, 75, 91, 98, 99.6 values. These represent separation of 0.67 SD and are therefore equally spaced with the 2 smallest and 2 largest centiles representing $\pm$ 2 and 3 SD respectively. The extra centiles are reported to provide a better guideline to indicate concern or referral (Cole, 1994). The new charts suggest that people in the UK appear to be growing taller and bigger, with the 50th centile values being about 1-1.5 cm greater. The data are more nationally representative in that the measurements were derived from seven UK sources on white children, whereas the Tanner children lived mostly in London and the Southeast. Tanner and Buckler (1997) subsequently revised their growth charts for height to allow for the secular trend, but kept the seven centiles and maintained a longitudinal component to cover the years of puberty, unlike the Child Growth Foundation charts which are based on cross-sectional data alone. A recent study supports the use of the British 1990 growth charts in preference to the old standards of Tanner and colleagues (1966), for cross sectional and longitudinal assessment of growth in primary school children (Rudolf et al, 2000). Recommendations have been made from an expert consensus group on the use of growth reference charts in the UK (RCPCH, 2001). They state that the UK 90 and thus the revised Tanner & Buckler (1997) reference data are both suitable for monitoring height, but that only the UK 90 reference should be used for assessing weight. Recently, growth charts specific for prepubertal children with CRI due to congenital disorders have been developed based on retrospective longitudinal data (Schaefer et al, 1996). These charts require validation, as they do not address other potential causes of growth failure and hence may falsely lower expectations for optimal growth.

Percentage ideal weight for height, gender and age, the preferred index for the WHO and the standards of the United States National Centre for Health Statistics (WHO working group, 1986), can be calculated by dividing the child's actual weight by the normal weight for their height. Observers plot their actual height on a growth chart to determine the height centile, determine the weight that corresponds to the same point on the centile chart as the height, and then divide actual weight by ideal weight and multiply by 100. Percent ideal body weight between 90-110% is considered normal. A child is considered to be at mild, moderate or severe risk of malnutrition if their percent ideal body weight is between 80-90%, 70-80% or <70% respectively. This method however, has been suggested to be unreliable as a measure of nutritional status, due to

large inter- and intra-examiner variability in estimated values (Poustie et al, 2000). The assumption that a child of given length or height has an ideal weight, irrespective of age has also been shown to be invalid (Cole, 1985). For those children who are short or tall and whose growth tracks their given percentiles for height and weight, would be seen to fall or increase respectively across weight-for-height percentiles. Cole (1985) recommended weight/ height^2 as an alternative indicator for nutritional status.

Use of the BMI [weight (kg)/height (m)^2] in adults has been linked with a classification system, based on associations between BMI and all cause mortality (International Obesity Task Force, 1998). These fixed classifications are not appropriate for children, in whom the 50th centile for BMI shows profound changes from birth through to early adulthood. Standardised curves for BMI centiles for children have since been devised (Cole et al, 1995), based on the same large population sample used for the new growth standards with the same 9 centile spread and calculated by the same formula. BMI centile charts of this data for both boys and girls have been published by the Child Growth Foundation and have recently been tested in clinical practice. They have been suggested to contain biases in infancy and early childhood but were felt to be a useful tool for estimating the prevalence of over- or under-nutrition during later childhood (Savage et al, 1999). BMI's for children have been confidently recommended for clinical application in the United Kingdom as long as care is taken not to confuse heavy musculature with obesity in a minority of children (Prentice, 1998). The distributions of weight for a given height are very different following the onset of puberty compared with pre-pubertal age ranges, and should be taken into consideration when using BMI or weight-for-height measures for early or late-maturing children (WHO, 1995). The use of dual-energy x-ray absorptiometry (DEXA) provides support for the use of BMI as a measure of body fatness in girls aged 4-16 years age (Goulding et al, 1996). The expert consensus group for use of growth reference charts in the UK (RCPCH, 2001) recommend that the UK 90 BMI reference can be used for assessing weight relative to height, but that weight for height should not be used. Caution however, should be placed in using the BMI charts due to the secular trend to increased childhood fatness.

Normal growth patterns are best demonstrated by growth velocity curves. Methods for assessing growth rates (velocity) differ between Europe and the United States, although growth patterns remain the same. British height velocities are expressed as growth rates

in centimetres per year derived from regression analyses over time (Tanner et al, 1966). In the United States, incremental growth tables are provided at 3-month intervals during the first year and at 6-month intervals thereafter (Roche & Himes, 1980; Baumgartner et al, 1986). Height increments or height velocity are difficult to compare when growth is retarded or when puberty is commencing. One method is to compare height velocity to that projected for normal children of the same height rather than the same age (Chantler & Holliday, 1973) or related to bone age rather than chronological age. There are no reference values however, for the distribution of height according to bone age in the normal population. Growth rate varies at different times of the year, with growth velocity being greatest in the spring and lowest in the winter, and hence it is difficult to assess growth performance satisfactorily over periods of less than one year (Marshall, 1971).

Standard deviation scores (SDS), also known as z scores (standard Normal deviate) for height, have been recommended to compare growth and growth velocity of children with CRI over specified intervals (Potter et al, 1978; Abitbol et al, 1996). SDS's can also be calculated for weight and BMI. Standard deviation scores are calculated by comparing the patient's actual value to the value for a normal child at the 50th percentile for the same chronological age and sex, and the difference is divided by the standard deviation of the value for the normal child, according to the formula:

$$\text{SDS} = \frac{\text{Patient's actual value} - \text{value at } 50^{\text{th}} \text{ percentile for a normal child}}{\text{Standard deviation (SD) of the value for a normal child}}$$

The SD is calculated from the difference between the value at the 5^{th} and 95^{th} percentile divided by 3.3. In an unaffected population, the mean SDS will have a value of zero and a SD of 1; the 95% confidence limits will be between -2 and + 2 SDS, corresponding to the 2^{nd} and 98^{th} centile. A value greater than +2 or less than –2 is likely to be associated with an abnormal increase or decrease in weight, height or BMI. The calculation allows comparison within small groups independent of age or sex. The problem with this method is that the standard deviation for height increases with age, so a child may actually have the same growth rate over a treatment period but show a reduced SDS for height. Similarly, the younger the child, the easier it is for the child to improve their SDS. As a result, growth velocity and growth velocity SDS's are more sensitive indicators of growth rates than changes in height SDS. The combined use of

change in SDS for height and of the SDS for growth velocity gives a clear assessment of what is happening in growth (Hellerstein et al, 1987). Growth in the renal failure patient with retarded development begins to accelerate at a time when the growth period of the average adolescent comes to an end. Thus, the height SDS in these children shows a transient fall, followed by an apparent 'recovery' phase. This 'artificial' variation severely limits the use of height SDS during puberty. The growth rate during the adolescent growth spurt is more marked than the change in height. In boys over 10 years and girls over 9 years of age therefore, height velocity SDS should not be used and height SDS should be used with caution.

Catch-up growth refers to compensatory growth upward towards a previously established or 'normal' growth channel. There is variability in growth and body composition in children from all populations. A single measurement of an individual's stature is therefore not sufficient to determine whether this represents failure-to-thrive or normal growth and nutritional status in a healthy, short child (WHO, 1995). The magnitude of growth loss and recovery is age dependent, being maximal during infancy and early childhood. When patient groups are considered, the average gain in height SDS is used to assess catch-up growth (Abitbol et al, 1996). Nutritional stunting may only be partly reversible, thus for children older than 5 years, small stature can be more a reflection of previous nutritional deprivation than of current nutritional status (WHO, 1995). It is not clear whether growth rates in children with CRI are best compared with those of normal children of similar chronological age, height age or bone age. Height age or bone age tend to be used more widely in research, for comparison of groups of individuals against parameters that vary with age, such as nutritional requirements. It is accepted that for comparing age-related factors, a height for chronological age that lies below the 2nd percentile (below -2 SDS) should be corrected to an age equivalent to that height on the 50th percentile.

Radiographs of hands and wrists obtained at 6 monthly intervals are useful to assess growth in relation to bone age (Raymond et al, 1990), as many children with more severe CRI exhibit delayed bone age. Bone age may be the most accurate on which to calculate certain nutritional requirements in children, rather than chronological or height age.

Triceps skinfold thickness (TSF) and MUAC are often used to assess body fat and muscle mass, by comparison to published standards, using the patient's height age as reference (Frisancho, 1974). MUAC and TSF standard curves are derived from cross-sectional, not longitudinal data and therefore the growth curve of an individual may vary considerably from standard curves. Accuracy is decreased if the child falls below the 5th percentile on the standard growth charts. MUAC is a composite measure of muscle, fat and bone. When MUAC is combined with the triceps skin-fold measurement, mid-arm muscle circumference (MAMC) and fat stores can be estimated (Frisancho, 1981). MAMC is estimated as follows:

MAMC (cm) = MUAC (cm) - [0.314 x TSF (mm)].

Assumptions that the composition of fat free mass is constant is invalid in children however, and changes in composition with age must be accounted for. A number of equations are available to estimate body fatness in children, but it has been suggested that they are associated with significant errors and should not be used for estimating total body fatness of prepubertal children at present (Reilly et al, 1995).

MUAC is obtained by placing a non-stretchable measuring tape around the midpoint of the non-dominant arm, which should hang freely, ensuring that the soft tissue is not compressed. The midpoint is estimated by the child placing their hand on their hip to flex the elbow at a right angle and measuring and marking the midpoint between the acromium process of the non-dominant scapula and olecranon process (elbow tip). Values should be recorded to the nearest 0.1cm. Arm anthropometry is non-invasive, cheap, easily measured and has a high degree of reproducibility. MUAC correlates well with weight-for-height (Carter, 1987) and was shown to be the best predictor of death secondary to malnutrition (Briend et al, 1986). MUAC is thus a useful substitute for assessing acute malnutrition, especially if fluid retention is suspected which would invalidate weight measures.

TSF should be measured at the same position using standardised, calibrated calipers such as Harpenden calipers. The arm should be relaxed and hanging freely and with the thumb and index finger approximately 2 cm apart, the skin should be pinched approximately 1 cm above the midpoint, so that the midpoint can be measured with the calipers. Care should be taken to exclude the underlying muscle (by flexing the child's arm) before the jaws of the calipers are applied to the skinfold, perpendicular to the

triceps. To obtain a stable measurement, the reading should be taken 3 seconds after the caliper is applied. The procedure should preferably be repeated 2 or more times until measurements agree within 0.2 mm and the final value recorded to the nearest 0.1 mm. Reproducibility is often poor and difficult in young children, especially with the use of calipers for skinfold thickness, which can cause discomfort. For an individual, the measurement error of a single measurement may be as large as the difference between percentile ranks. For example, the intra-individual technical error of measurement for children 6-11 years old for a TSF measurement was found to be 0.8 mm, whereas the inter-individual measurement error was 1.9 mm (Ulijaszek & Lourie, 1994). Accuracy is increased if the same examiner performs the anthropometric measurements three times at each site using standard technique and properly calibrated equipment; the median of these measurements being recorded.

Reliable anthropometric measures other than growth are necessary to establish nutritional status in adults. A simple and reliable method is that of Subjective Global Assessment (SGA), a classification system for nutritional risk based on the findings of subjective and objective aspects of a medical and dietary history in combination with a physical examination, as described by Detsky et al (1987). SGA is easy to perform, has low inter- and intra-observer variability and does not require sophisticated equipment. SGA has been associated with the probability of survival in adults on peritoneal dialysis (Churchill et al, 1996). The use of SGA has been developed further, due to concerns over the semiquantitative nature of the tool, restricting reliability and precision (Kalantar-Zadeh et al, 1999). The dialysis malnutrition score thus developed consists of seven variables: weight change (BMI), dietary intake, gastrointestinal symptoms, functional capacity, comorbidity, subcutaneous fat (TSF) and signs of muscle wasting (calculated MAMC). Each component is assigned a score from 1 (normal) to 5 (very severe). This score was suggested to be superior to SGA in the assessment of malnutrition in a group of haemodialysis patients (Kalantar-Zadeh et al, 1999), but it requires further validation.

The SGA has not been validated as a means of nutritional assessment in children and therefore should not be used for this purpose. The DOQI guidelines for Nutrition (NKF-DOQI, 2000) recommend development of a standardised nutritional assessment tool for children comparable to SGA, although this would need to be more complex due

to age and gender related changes in body composition and physical appearance. Conditions that may dictate a more frequent evaluation of the nutrition care plan could include dry-weight loss, ongoing decrease in oral intake, change in gastrointestinal function, significant change in SDS e.g. a 0.25 decrease in SDS for height, suboptimal laboratory values, concern for appropriate compliance with recommendations, or changes in psychosocial situation (NKF-DOQI, 2000).

Other methods of body composition assessment include isotope dilution methods, bioelectrical methods and bone densitometry. Most of these methods however require expensive facilities, expertise in their use and substantial patient co-operation, making them impractical for clinical practice. Isotope dilution methods involve the use of stable isotopes and the classic dilution principle to estimate the size of various compartments of the body. Deuterium oxide ($^{2}H_2O$) or oxygen-18 (^{18}O) are naturally occurring stable isotopes used in the research setting to safely and effectively measure the size of the total body water in infants and children (Schoeller et al, 1980).

Bioelectrical methods are based on the fact that water and electrolytes in the body have electrical properties that can be measured for estimation of total body water or fat-free mass. Devices are available that either measure total body electrical conductivity or the impedance of a low-energy electric signal as it passes through the body. Bioelectrical impedance analysis (BIA) is a non-invasive, safe and simple method (Lukaski, 1986), but controversy exists as to the accuracy of this tool, as significant errors have been noted in patients with disturbed fluid or electrolyte balance (Khaled et al, 1988). BIA requires the patient to be in a supine position with electrodes on exposed feet and arms and should not be measured until 20-30 minutes after termination of a dialysis session, due to its dependence on body water volume. BIA has been shown to correlate closely with skinfold measures for assessing lean body mass in children with renal disease (Stefanidis et al, 1996), whereas Kerr et al (1996) found it to be unreliable in the estimation of lean body mass in adult patients with ESRD. The manufacturers' software prediction equations should be used with caution, as they are based on normal volunteers and therefore may be inappropriate in the clinical setting. Further research is required to determine the validity of BIA, and hence is not currently recommended as a clinical tool for assessing body composition in patients with end stage renal disease (NKF-DOQI, 2000).

Near infra-red (NIR) measurements have been proposed by Kalantar-Zadeh et al (2001) for the future, for the longitudinal assessment of nutritional status in dialysis patients. NIR is non-invasive, quick and convenient and is resistant to the effect of volume changes observed in dialysis patients. It is based on principles of light absorption and reflection using near-infrared spectroscopy and involves placement of the NIR sensor on an exposed upper arm for a few seconds, whilst the patient is sitting upright. Body fat is measured and the computer calculates lean body mass and total body water. Dual photon absorptiometry and dual-energy x-ray absorptiometry (DEXA) (Prentice, 1995) are techniques that measure three compartments of the body: bone mineral mass and density, lean body mass and fat mass, all which possess varying densities and hence attenuate the beams differentially. DEXA is reported to be an accurate measure unaffected by variations in hydration, involving low radiation exposure, but is therefore a more invasive method than NIR. Compared to BIA, NIR and anthropometric methods however, DEXA has the added advantage of being independent of sample-based prediction equations (Zemel et al, 1997).

2.3 Biochemical markers

Total serum proteins, serum albumin, pre-albumin, transferrin, complement fractions, immunoglobulins, amino acid levels and other serum components have been evaluated for assessment of nutritional status in patients with CRI (Wardle et al, 1975). Total serum protein and/or serum albumin and transferrin appear to be most useful in children with CRI (Hellerstein et al, 1987), although serum albumin and transferrin are not always sensitive to changes in nutritional status and often fail to correlate with other nutritional parameters (Blumenkrantz et al, 1980).

Decreases in serum albumin and transferrin are considered to reflect a decrease in visceral protein mass, which relates to proteins synthesised by the liver and other viscera. Albumin is the most abundant plasma protein, functioning to maintain plasma oncotic pressure, and serving as a major carrier protein for drugs, hormones, enzymes and trace elements. The main function of transferrin is to bind ferrous iron and to transport iron to the bone marrow. Serum transferrin has a shorter half-life of about 8-9 days compared to serum albumin with a half-life of about 18-20 days. Serum transferrin has therefore been suggested to be a more sensitive marker of protein energy malnutrition (PEM) than serum albumin (Heymsfield et al, 1994). Plasma albumin

concentration is a powerful predictor of outcome in patients with ESRD (Lowrie & Lew, 1990), which may not only reflect protein malnutrition, but also the influence of non-nutritional factors such as overhydration, proteinuria and decreased synthesis from inflammation, infection, and acidosis. These non-nutritional factors may themselves carry an increased risk of death (Bergstrom, 1995). Positive acute-phase reactants (e.g. C-reactive protein [CRP], alpha-1 acid glycoprotein [α1-AG] and ferritin) may be used to identify the presence of inflammation (Docci et al, 1990), although α1-AG may be more specific than CRP for detecting inflammation in dialysis patients. As a result, concern exists in using serum albumin as an isolated marker in the classification of nutritional status. Serum transferrin can also be affected by other factors, such as iron deficiency which increases transferrin, or iron loading which may decrease the serum concentrations (Lane, 1966). In dialysis patients therefore, the increased iron requirements induced by erythropoietin therapy may complicate interpretation of serum transferrin concentrations.

Serum albumin measured by the dye binding method of bromocresol green (BCG) is currently the most frequently used assay in clinical chemistry laboratories throughout the UK. It may however, overestimate albumin levels in individuals (Wells et al, 1985; Heymsfield, 1994), due to variable binding of the dye by globulins, the error being proportionally greater at lower serum albumin concentrations. The more accurate bromocresol purple (BCP) method accepts as normal an albumin level approximately 5g/l lower than the normal reference range for BCG (Blagg et al, 1993). It is therefore important to be aware of which laboratory method is being used prior to evaluation of nutritional status (Asbell, 1994). Lowrie and Lew (1990) measured serum albumin levels by the BCG method, quoting normal values to be between 38-50 g/l. The relative risk of death in haemodialysis patients was noted to be twice that of the reference group in patients with values between 35-40 g/l and five times that in those with concentrations between 30-35 g/l. Despite good agreement between the BCP and electroimmunoassay method (EIA) in non-renal failure hospitalised patients [EIA being proposed to be the reference method for serum albumin (Pascucci et al, 1983)], the BCP method tended to underestimate serum albumin levels in some children receiving chronic haemodialysis (mean value of 30.8 g/l compared to a predicted value of 38.5 g/l), whereas the BCG method did not (Wells et al, 1985). It is suggested that an

interfering factor is present in the serum of some haemodialysis patients, which affects the binding of BCP to albumin but does not similarly affect BCG.

Retinol binding protein (RBP) is bound to prealbumin (thyroxin-binding prealbumin or transthyretin) in a 1:1 ratio and is filtered and reabsorbed by the kidney. The function of prealbumin is to transport thyroxine and serve as a carrier protein for RBP and hence vitamin A. Prealbumin and RBP are synthesised in the liver and have short half-lives of 2 days and 12 hours respectively, and hence have been considered to be more sensitive than albumin as an indicator of nutritional status. Prealbumin and RBP respond acutely to energy and/or protein intakes and are therefore felt to be more useful as an early indicator of adequate/inadequate nutritional intake (Ingenbleek et al, 1994) than an accurate measure of overall nutritional status (Farthing, 1983). Prealbumin and RBP increase with age and in CRI due to impaired degradation of the prealbumin-RBP complex by the kidney (Cano et al, 1988), and are therefore suggested to be unsuitable indicators of protein intake in these circumstances (Wardle et al, 1975). Adjustment can be made for an altered physiological range in patients with a stable degree of renal failure such as chronic haemodialysis patients, such that concentrations of prealbumin can be correlated with nutritional status (Cano et al, 1988), noting trends in direction with time (Zazra, 1997). A concentration < 30 mg/dl (normal range 10-40 mg/dl) may indicate malnutrition in the adult haemodialysis patient (Sreedhara et al, 1996). Prealbumin has been shown to be inversely related to mortality in maintenance adult haemodialysis patients, with a relative risk reduction of 6% per 1 mg/dl rise in prealbumin, which is independent of serum albumin concentrations (Chertow et al, 2000). Duggan and Huffman (1998) extend caution to the interpretation of prealbumin levels in patients who urinate more than 240 ml per day, as they were found to have lower prealbumin and creatinine levels. This may be particularly relevant to the paediatric population, many who tend to have significant residual renal function, and along with prealbumin levels increasing with age will confound the use of prealbumin as a marker of nutritional status in paediatrics.

Prealbumin is not significantly influenced by fluctuations in hydration status but similarly to albumin and transferrin, prealbumin and RBP are both negative acute-phase reactants. RBP is affected by vitamin A deficiency, hyperthyroidism, zinc deficiency and liver disease. The number of factors that can alter the synthesis, degradation,

compartmentalisation and hence serum levels of these proteins, probably accounts for much of the variability of results in published reports (Blumenkrantz et al, 1980). Prealbumin has been found to correlate with other established nutrition assessment parameters such as serum albumin, creatinine and cholesterol and has been shown to be an independent predictor of morbidity and mortality in the haemodialysis patient (Avram et al, 1995). The recent nutrition NKF-K/DOQI guidelines however, suggest that there is insufficient evidence to conclude that prealbumin is a more sensitive or accurate index of malnutrition than serum albumin (NKF-K/DOQI, 2000).

Insulin-like growth factor-1 (IGF-1) is one of the somatomedins, which are low-molecular weight peptides produced by the liver, controlled by growth hormone and which act as regulators of cell growth. IGF-1 has a half-life of a few hours and may be a useful indicator of nutritional status as it is thought not to be affected by the acute-phase response (Unterman et al, 1985). IGF-1 has been shown to correlate with other serum protein markers (Minuto, 1989) but only a poor correlation was found between IGF-1 and anthropometric measurements (McWhirter et al, 1995). IGF-1 levels fall during fasting and increase with refeeding. The assay for IGF-1 was not available for this study.

The strongest predictors of death in adult haemodialysis patients have been shown to be low levels of serum albumin (protein malnutrition), serum creatinine (low muscle mass and protein intake) and low urea reduction ratios (Lowrie and Lew, 1990; Owen et al, 1993; Goldwasser et al, 1993a). Several studies have demonstrated that low prealbumin concentrations (< 30 mg/dl) are associated with increased mortality risk and correlate with other indices of PEM (Goldwasser et al, 1993b; Avram et al, 1995; Sreedhara et al, 1996). Serum urea (U-shaped profile with high levels suggesting under-dialysis and low levels suggesting under-nutrition) and low levels of serum cholesterol suggestive of energy depletion are also reported to be risk factors for increased mortality in adults receiving haemodialysis (Lowrie & Lew, 1990; Goldwasser 1993a).

Creatinine clearance was shown to be significantly associated with serum transferrin levels in adults with CRI, where the serum transferrin level decreased by 16.7 mg/dl for each 10 ml/min decrease in creatinine clearance (Ikilzer et al, 1995). No association however, was found between GFR and serum albumin, cholesterol and prealbumin,

although most nutritional indices were found to deteriorate as creatinine clearance and protein intake decreased. This may be a reflection upon the degree of severity of CRI, as the majority of studies that highlight serum albumin as being a marker of increased mortality have been undertaken in patients undergoing dialysis. The American nutrition guidelines for children on dialysis (NKF-K/DOQI, 2000) state that serum albumin concentration is considered to be one of the most useful measures of protein-energy nutritional status in dialysis patients, whereas serum transferrin may have an advantage over albumin in predialysis patients not receiving EPO.

Serum ferritin concentrations have been found to decrease markedly once rhuEPO is commenced (Eschbach et al, 1989; Krmar et al, 1997). In adult patients, it has been suggested that serum ferritin concentrations are the most reliable in monitoring body iron stores in the prevention of absolute iron deficiency during rhuEPO therapy (Hussein et al, 1975). It has also been demonstrated that serum ferritin levels are the best predictors of the development of iron deficiency anaemia in children with CRI (Morris et al, 1994). Morris et al, (1994) recommend that children with a serum ferritin of 60μg/l or less and those who develop a falling MCV during rhuEPO treatment should receive high-dose oral iron supplementation before and during treatment with rhuEPO. The NKF-DOQI guidelines (1997) recommend, in accordance with Eschbach and colleagues (1989), that iron status should be monitored by serum ferritin and percent transferrin saturation (TSAT). Transferrin carries and donates iron to the sites of haemoglobin synthesis and as such, percent transferrin saturation is a good indicator of iron available for erythropoiesis i.e. a marker of functional iron deficiency. TSAT is calculated as serum iron /total iron binding capacity (TIBC) x 100, or serum iron (μg/dl) x 70.9/ transferrin concentration (mg/dl) (Bainton & Finch, 1964). TIBC is inversely related to the amount of iron store and its level is affected before the iron supply fails. There is however day to day variation (Sundeer-Plassman & Horl, 1995), and the concentration of transferrin varies with nutrition in parallel with serum albumin (Kalantar-Zadeh et al, 1998). Sufficient iron should be administered to maintain a TSAT of 20% or more and a serum ferritin level of 100 μg/l, although during inflammation, ferritin, percentage hypochromic red cells or TSAT may be normal, but iron is not available. Some measure of acute phase reaction such as the C-reactive protein will aid in this diagnosis. Patients with CRI are unlikely to respond to further

iron doses if the TSAT increases to above 50% and/or the serum ferritin level increases to 800 μg/l.

Percentage hypochromic red cells; an indirect marker of how much iron is getting into the red cell, is also suggested to be diagnostic of iron deficiency anaemia (Macdougall, 1992b). The European guidelines for anaemia (ERA/ EDTA, 1999) preferentially recommend measurement of percentage hypochromic cells over TSAT as the more reliable marker of functional iron deficiency. In normal individuals, the proportion of hypochromic red blood cells is < 2.5% and a proportion > 10% is strongly suggestive of functional iron deficiency. The European guidelines state that to achieve minimum targets of serum ferritin ≥ 100 μg/l and hypochromic cells <10% (or TSAT >20%), management will require aiming for optimal levels of serum ferritin between 200-500 μg/l and hypochromic cells < 2.5% (or TSAT of 30-40%).

The NKF-DOQI (1997) guidelines recommend that TSAT and ferritin should be checked every month in patients not receiving iv iron whilst attempting to achieve an acceptable haematocrit, and at least once every 3 months in those not receiving iv iron, following attainment of adequate serum haemoglobin levels. Intravenous iron should be discontinued for two weeks prior to performing these measurements of iron status. A new test for the evaluation of iron status is also available but not yet widely used and that is the measurement of serum transferrin receptor (Cook et al, 1993). Its concentration is depressed in all conditions of decreased red cell production with the exception of iron deficiency, in which it is elevated.

Querfeld (1993) recommends that serum lipids, especially triglycerides in children should be compared with normal values adjusted for age and sex, as levels differ considerably from normal adult levels. Older children are recommended to fast overnight prior to blood sampling for lipids, whereas in younger children, fasting for at least 4 hours appears to be acceptable in practice (Kari et al, 1998). Hyperlipidaemia, often associated with CRI is known to cause a variety of errors in the biochemical analysis of serum, such as depression of serum electrolyte concentrations, due to a space-occupying effect of lipids in the sample. Serum lipids can also interfere with colorimetric assays, resulting in falsely elevated values of plasma constituents. Hyperlipidaemia has been reported to result in overestimation of inorganic phosphorus

values (Wentz et al, 1976), the degree of overestimation correlating positively with serum triglyceride concentration, which resulted in inappropriate prescription of phosphate binders (Leehey et al, 1985). As a result, the degree of hyperlipidaemia present should be taken into account when interpreting serum phosphate concentrations in children with CRI and the possible questioning of compliance to phosphate restricted diets and phosphate binders.

Chapter Three

PATIENTS AND METHODS

3.1 Overview

There are few published reports detailing the practical dietary advice that should be prescribed to achieve the nutritional recommendations described by various groups for children with CRI (Hellerstein et al, 1987; Yang et al, 1988-89; Sedman et al, 1996). This two year prospective study was thus designed to evaluate the current practical 'package of care' of joint medical and dietetic intervention, provided to children with CRI and their families within a specialist paediatric renal unit. Such information should be invaluable in contributing towards the future development of practical clinical guidelines for the management of children with varying levels of severity of CRI.

3.2 Ethics

All children requiring a formal GFR measurement were sent an information sheet inviting the family to participate in the study, together with their appointment, by the day case co-ordinator. Informed consent was obtained by one of two dietitians (LN, JC) from one of the parents and/or child on the day of ward attendance for the GFR. The study was designed such that the frequency of monitoring would be in accordance with usual clinical practice for severity of CRI. For this reason, those who were subsequently found to have a GFR >75 ml/min/1.73m^2 could not provide more than baseline data due to their infrequent follow-up. The study was approved by Nottingham City Hospital research ethics committee.

3.3 Patients

All children requiring a GFR measurement between July 1996 and December 1998 were asked to participate, with the exception of those with congenital growth abnormalities and those on dialysis. All children/carers who were asked, agreed to participate at the outset. The GFR was measured by estimating the clearance from plasma of ^{51}Cr labelled EDTA (section 4.2). 125 children (73 boys, 52 girls) were subsequently grouped according to their GFR, in accordance with the classification used for the NAPRTCS data (Fivush et al, 1998). 27 children (15 male) had mild CRI (GFR 50-75 ml/min/1.73m^2; Table 3.3.1), 21 children (16 male) had moderate CRI (GFR 25-50 ml/min/1.73m^2; Table 3.3.2), 19 children (12 male) had severe CRI (GFR< 25 ml/min/1.73m^2; Table 3.3.3) and 58 children (30 male) had 'normal' kidney function (GFR>75 ml/min/1.73m^2; Table 3.3.4). This classification remained for each child throughout the two year period, irrespective of whether their kidney function deteriorated. The proportion of children that changed groups during the study is illustrated in tables 4.3.5.2 - 4.3.5.4 (appendix 1) for mild to severe CRI respectively, although this was only determined based on estimations of GFR and not from ^{51} Cr-EDTA measurements.

All children were under medical supervision prior to recruitment, whereas although a majority of children with severe CRI were under dietetic review (89%), only 67% of children with moderate, 33% with mild CRI and 4% with 'normal' renal function were receiving dietetic supervision. The results are misleading however, because they are not a true reflection of regular dietetic review. Once children have been referred to the paediatric renal dietitian, even for an acute episode, they are not discharged from the dietetic caseload until transfer to an adult unit or other paediatric renal centre, as re-referral is reasonably common. This is the case in children admitted with HUS, where they are managed acutely by the dietitian but are not usually followed up in the long-term, which is of particular relevance to this study. A large proportion of the control group (52%) and 22% of those with mild CRI were identified for this study as a result of being part of a follow-up study in HUS patients, involving formal GFR assessments at 1, 5 and 10 years post illness (Small et al, 1999). These children are highlighted in the relevant tables, and the revised figures would suggest that only 2 (3%) of children with 'normal' renal function, 4 (15%) with mild and 12 (57%) with moderate CRI were

actually receiving ongoing dietetic supervision prior to the start of this study, compared with 89% in those with severe CRI.

Children in the 'normal' group were not receiving prescribed medications at baseline, whereas 9 children (33%) with mild CRI (Table 3.3.5), 10 children (48%) with moderate CRI (Table 3.3.6) and all those with severe CRI (Table 3.3.7) were in receipt of medications or dietetic products. None were being treated with growth hormone, corticosteroids or immunosuppressants. The majority of medications used in children with mild CRI were related to micronutrient supplements. In those with mild CRI, 4 of the children not in receipt of dietetic follow-up were taking an OTC vitamin supplement, 3 children were prescribed an iron supplement and one child (the youngest) required a glucose polymer to supplement energy intake. In children with moderate CRI, 2 children were prescribed a glucose polymer of which one child (44) had just been transferred to the study unit and hence was not known to the dietitian prior to the study. This was also the case for one child (39) in receipt of a prescribed vitamin supplement. The youngest child in the group (37) was also the only one in the group to need a sodium supplement. Three children with moderate CRI were prescribed alfacalcidol prior to the study, whereas a majority (89%) of children with severe CRI required alfacalcidol, calcium carbonate or both to prevent the development of secondary hyperparathyroidism. Almost half of those with severe CRI were in receipt of a nutritional supplement, although only one child (62) was prescribed a complete enteral feed, which was administered via a gastrostomy button. Half of the group was also prescribed a vitamin supplement, and a separate oral iron preparation. Only one of the 9 children requiring medications to control hypertension was not in receipt of an ACE inhibitor as part of the treatment. A third of those with severe CRI required sodium bicarbonate to treat metabolic acidosis.

The complete data set described above is used throughout the thesis. Food diaries however, were only received for assessment from 35 (60%) of the children with 'normal' kidney function, whereas 85% of diaries were returned from those with mild CRI, and 90-95% of those with moderate and severe CRI returned their diaries. At editorial request, the baseline data set were re-analysed for only those children who had completed a food diary, to eliminate missing data in the baseline comparison of dietary intakes with nutritional and biochemical parameters between children with differing

levels of severity of renal function (Norman et al, 2000). Baseline demographic data in this subset therefore differs, with observations described on a total of 95 children; 35 children with 'normal' kidney function, 23 with mild CRI, 19 moderate CRI and 18 with severe CRI.

Table 3.3.1 Baseline demographic data of 27 children with mild CRI

Patient number	Sex (M/F)	Age (yrs)	GFR	Previous dietetic supervision (yrs)	Protein: creatinine (g/mmol)	Primary Disease
1	M	3.8	64	0	0.01	HUS
2	F	16.4	73	0	0.01	RN
3	M	12.7	62	0	0.01	O
4	M	5.4	61	0	0.01	OBS
5	F	4.2	73	0	0.01	HUS
6	F	2.8	64	0	0.02	HUS
7	M	3.8	52	0	0.01	RN
8	M	4.8	74	5 *	0.01	OBS
9	F	10.6	57	0	0.01	RN
10	F	16.9	52	0	0.02	RN
11	M	7.1	69	0	0.01	OBS
12	F	14.8	59	0	0.01	RN
13	M	5.0	71	5 *	0.03	RN
14	M	9.0	55	5.4 *	0.01	HUS
15	F	11.2	73	0	0.01	RN
16	F	5.1	66	1 *	0.01	RN
17	M	11.2	67	0	0.01	RN
18	M	9.5	64	5.6 *	0.02	HUS
19	F	13.5	54	0.5	0.01	DYS
20	M	13.8	61	5.5	0.01	OBS
21	M	11.7	53	0	0.01	RN
22	F	7.6	52	4.5	0.03	OBS
23	F	14.6	70	0	0.02	O
24	M	2.0	51	0.5	0.69	DYS
25	F	6.6	53	1 *	0.01	HUS
26	M	7.8	63	0	0.16	O
27	M	6.3	70	0	0.01	RN
Summary	**56% M**	**8.8**	**62**	**n=9; (33%) mean 1.3yrs**	**n=2; (7%)**	**41% RN 19% OBS**

GFR, Glomerular filtration rate; HUS, Haemolytic Uraemic Syndrome;
OBS, Obstructive nephropathy; RN, Reflux nephropathy; O, Other;
DYS, Hypo/dys plastic kidney; GN, Glomerular nephritis/nephropathy

Summary
Means given for age, GFR, dietetic supervision
Number and % of sample given for sex, dietetic supervision, protein: creatinine ≥ 0.1 g/ mmol (denotes substantial proteinuria), and the predominant primary disease
* Have not seen a dietitian since their initial illness/ assessment

Table 3.3.2 Baseline demographic data of 21 children with moderate CRI

Patient number	Sex (M/F)	Age (yrs)	GFR	Previous dietetic supervision (yrs)	Protein: creatinine (g/mmol)	Primary Disease
28	M	11.9	47	0	0.02	O
29	M	5.7	36	0	0.11	RN
30	F	16.1	40	8.6	0.01	RN
31	M	5.5	38	0	0.02	OBS
32	M	15.9	33	6.5	0.20	OBS
33	M	2.1	42	2	0.04	DYS
34	F	3.2	48	1 *	0.23	HUS
35	M	9.7	31	6	0.16	DYS
36	M	2.3	42	1	1.00	O
37	M	2.0	26	2	0.58	RN
38	M	9.4	26	9.5	0.01	OBS
39	F	13.0	48	0	0.01	RN
40	M	10.8	36	10.5	0.03	DYS
41	M	10.1	47	1	0.02	OBS
42	M	13.4	35	0	0.02	OBS
43	M	12.0	26	0	0.07	RN
44	F	5.7	31	0	0.01	RN
45	M	6.6	27	4.7	0.20	RN
46	F	11.7	41	6	0.38	RN
47	M	6.8	49	4.3 *	0.01	HUS
48	M	5.1	45	5	0.02	RN
Summary	**76% M**	**8.5**	**38**	**n=14; (67%) mean 3.2 yrs**	**n=8; (38%)**	**43% RN 24% OBS**

GFR, Glomerular filtration rate; HUS, Haemolytic Uraemic Syndrome;
OBS, Obstructive nephropathy; RN, Reflux nephropathy;
DYS, Hypo/dys plastic kidney; GN, Glomerular nephritis/nephropathy.
O, other

Summary
Means given for age, GFR, dietetic supervision
Number and % of sample given for sex, dietetic supervision, protein: creatinine ≥ 0.1 g/ mmol (denotes substantial proteinuria), and the predominant primary disease

* Have not seen a dietitian since their initial illness

Table 3.3.3 Baseline demographic data of 19 children with severe CRI

Patient number	Sex (M/F)	Age (yrs)	GFR	Previous dietetic supervision (yrs)	Protein: creatinine (g/mmol)	Primary Disease
49	F	7.1	22	3.9	0.02	O
50	M	4.6	12	4.5	0.12	DYS
51	M	8.4	19	7	0.15	HUS
52	F	16.0	16	10	0.06	RN
53	M	8.6	23	0.5	0.01	OBS
54	M	11.4	24	0	0.12	RN
55	M	15.5	12	2.3	0.25	RN
56	M	7.3	10	7.3	0.16	O
57	F	12.0	16	0.8	0.27	RN
58	F	14.9	24	2	0.09	RN
59	F	10.3	14	8.4	0.34	HUS
60	F	11.4	22	2.4	0.13	RN
61	M	12.1	14	10	0.05	OBS
62	M	2.7	7	2.5	0.33	DYS
63	M	13.4	22	2.5	0.11	OBS
64	M	12.3	15	0.5	0.09	DYS
65	F	13.8	19	4	0.01	RN
66	M	10.3	20	0	0.33	DYS
67	M	2.0	24	2	0.11	OBS
Summary	**63% M**	**10.2**	**18**	**n=17; (89%) mean 3.7 yrs**	**n=12; (63%)**	**39% RN 22% OBS**

GFR, Glomerular filtration rate; HUS, Haemolytic Uraemic Syndrome;
OBS, Obstructive nephropathy; RN, Reflux nephropathy;
DYS, Hypo/dys plastic kidney; GN, Glomerular nephritis/nephropathy.
O, other

Summary
Means given for age, GFR, dietetic supervision
Number and % of sample given for sex, dietetic supervision, protein: creatinine ≥ 0.1 g/ mmol (denotes substantial proteinuria), and the predominant primary disease

Table 3.3.4 Baseline demographic data of 58 children with 'normal' renal function

Patient number	Sex (M/F)	Age (yrs)	GFR	Previous dietetic supervision (yrs)	Protein: creatinine (g/mmol)	Primary Disease
68	F	10.2	111	0	0.86	GN
69	M	5.8	112	0	0.06	HUS
70	F	14.1	114	0	0.27	HUS
71	F	5.3	116	0	0.01	HUS
72	F	9.3	133	0	0.01	HUS
73	F	6.9	104	0	0.01	HUS
74	M	6.8	100	0	0.01	HUS
75	M	15.4	80	0	0.01	RN
76	F	6.8	119	0	0.01	HUS
77	F	6.4	170	0	0.01	RN
78	M	11.0	76	0	0.01	RN
79	M	2.0	111	0	0.01	ON
80	M	5.4	109	0	0.01	RN
81	M	4.0	114	1 *	0.01	HUS
82	F	15.4	112	0	0.04	GN
83	M	5.0	166	0	0.01	RN
84	F	7.0	109	5 *	0.01	HUS
85	M	4.9	81	0	0.03	RN
86	F	7.0	114	0	0.01	HUS
87	F	5.2	111	5	0.01	RN
88	M	10.0	99	0	0.01	O
89	M	2.2	110	0	0.01	HUS
90	F	8.0	104	0	0.01	HUS
91	F	9.8	88	0	0.07	HUS
92	M	16.2	79	0	0.01	HUS
93	M	3.9	90	0	0.01	HUS
94	F	10.8	109	0	0.11	O
95	M	9.4	93	0	0.01	HUS
96	M	5.6	83	0	0.01	RN
97	M	5.0	109	0	0.01	RN
98	M	4.1	104	0	0.03	HUS
99	M	5.0	90	0	0.01	RN
100	F	3.3	95	0	0.01	HUS
101	F	8.2	106	0	0.01	RN

Table 3.3.4 Baseline demographic data of 58 children with 'normal' renal function

Patient number	Sex (M/F)	Age (yrs)	GFR	Previous dietetic supervision (yrs)	Protein: creatinine (g/mmol) *	Primary Disease
102	F	9.3	102	0	0.01	HUS
103	F	9.9	123	0	0.01	HUS
104	M	5.3	85	0	0.01	O
105	M	8.3	120	4.5	0.01	RN
106	F	11.0	92	0	0.01	RN
107	M	5.0	84	0	0.01	RN
108	M	6.6	101	0	0.01	HUS
109	F	7.8	145	0	0.01	HUS
110	F	7.8	112	0	0.01	HUS
111	M	14.0	101	0	0.33	GN
112	M	13.8	83	0	0.01	RN
113	F	14.0	92	0	0.01	RN
114	F	10.0	81	0	0.01	O
115	M	9.2	136	0	0.01	HUS
116	M	3.8	128	0	0.01	HUS
117	F	2.9	118	0	0.01	HUS
118	F	2.3	111	0	0.01	HUS
119	F	4.6	114	0	0.01	HUS
120	M	10.7	82	0	0.04	OBS
121	M	8.8	91	0	0.03	HUS
122	F	5.3	113	0	0.01	RN
123	F	7.4	83	0	0.03	HUS
124	M	6.2	103	0	0.01	RN
125	M	4.6	125	0	0.01	O
Summary	**52% M**	**7.7**	**106**	**n=4; (7%) mean 0.3yrs**	**n=4; (7%)**	**52% HUS**

GFR, Glomerular filtration rate; HUS, Haemolytic Uraemic Syndrome;
OBS, Obstructive nephropathy; RN, Reflux nephropathy;
DYS, Hypo/dys plastic kidney; GN, Glomerular nephritis/nephropathy
O, Other

Summary
Means given for age, GFR, dietetic supervision
Number and % of sample given for sex, dietetic supervision, protein: creatinine ≥ 0.1 g/ mmol (denotes substantial proteinuria), and the predominant primary disease

* Have not seen a dietitian since their initial illness

Table 3.3.5 Prescription of medical and dietetic therapies at baseline in 27 children with mild CRI

Patient number	Nutritional suppl	Vitamin suppl	Anaemia Rx	Bone Rx	BP Rx	Sodium suppl
1						
2						
3						
4			Iron			
5						
6		OTC				
7		OTC				
8		OTC				
9					Ca-ch β-blocker ACEI	
10						
11						
12						
13						
14						
15						
16						
17						
18						
19		Kt	Iron			
20						
21						
22			Iron			
23					ACEI	
24	Glucose P	OTC				
25						
26						
27						
Summary	N=1, 4%	N=5, 19%	N=3, 11%		N=2, 7%	

Key:

Glucose P, Glucose polymer; CEF, complete enteral feed; MS, milk substitute;
OTC, Over the counter vitamin supplement; Kt, Ketovite tablet;
Iron, Oral iron supplement; EPO, erythropoietin;
1-Alpha, Alfacalcidol; CaCO3, Calcium carbonate;
Ca-ch, Calcium channel blocker; β-blocker, Beta-blocker; ACEI, ACE inhibitor;
NaCl, Sodium Chloride; NaHCO3, Sodium bicarbonate

Table 3.3.6 Prescription of medical and dietetic therapies at baseline in 21 children with moderate CRI

Patient number	Nutritional suppl	Vitamin suppl	Anaemia Rx	Bone Rx	BP Rx	Sodium suppl
28						
29						
30		Kt				
31						
32						
33						
34					ACEI	
35						
36						
37	Glucose P		Iron			NaCl
38		Kt		1-Alpha		
39		Kt			Ca-Ch ACEI	
40						
41						
42						
43			Iron		β-blocker	
44	Glucose P					
45		Kt	Iron	1-Alpha		
46				1-Alpha	ACEI	
47		OTC				
48						
Summary	N=2, 10%	N=4, 19%	N=3, 14%	N=3, 14%	N=4, 19%	N=1, 5%

Key:

Glucose P, Glucose polymer; CEF, complete enteral feed; MS, milk substitute;
OTC, Over the counter vitamin supplement; Kt, Ketovite tablet;
Iron, Oral iron supplement; EPO, erythropoietin;
1-Alpha, Alfacalcidol; CaCO3, Calcium carbonate;
Ca-ch, Calcium channel blocker; β-blocker, Beta-blocker; ACEI, ACE inhibitor;
NaCl, Sodium Chloride; NaHCO3, Sodium bicarbonate

Table 3.3.7 Prescription of medical and dietetic therapies at baseline in 19 children with severe CRI

Patient number	Nutritional suppl	Vitamin suppl	Anaemia Rx	Bone Rx	BP Rx	Sodium suppl
49	Glucose P	Kt	Iron	1-Alpha		NaHCO3
50	MS	Kt				
51	Glucose P	Kt	Iron	1-Alpha CaCO3	ACEI	
52		Kt		1-Alpha	ACEI	
53				CaCO3	ACEI	
54				1-Alpha		
55			Iron	1-Alpha CaCO3	ACEI	
56	Glucose P	Kt	Iron	1-Alpha		NaHCO3
57	Glucose P		Iron	1-Alpha	Ca-ch β-blocker	
58		Kt	Iron	1-Alpha		
59	MS			1-Alpha		
60				CaCO3	Ca-ch β-blocker ACEI	
61	Glucose P	Kt		1-Alpha		NaHCO3
62	CEF MS	Kt		1-Alpha CaCO3		NaHCO3
63		Kt		1-Alpha	ACEI	NaHCO3
64			Iron EPO	1-Alpha CaCO3		
65					Ca-ch β-blocker ACEI	
66				1-Alpha	ACEI	
67	Glucose P		Iron	1-Alpha		NaHCO3
Summary	N=9, 47%	N=9, 47%	N=8, 42%	N=17, 89%	N=9, 47%	N=6, 32%

Key:

Glucose P, Glucose polymer; CEF, complete enteral feed; MS, milk substitute;
OTC, Over the counter vitamin supplement; Kt, Ketovite tablet;
Iron, Oral iron supplement; EPO, erythropoietin;
1-Alpha, Alfacalcidol; CaCO3, Calcium carbonate;
Ca-ch, Calcium channel blocker; β-blocker, Beta-blocker; ACEI, ACE inhibitor;
NaCl, Sodium Chloride; NaHCO3, Sodium bicarbonate

3.4 Methods

3.4.1 Assessment of dietary intake

Dietary advice for children with CRI is based on the nutritional intakes recommended for the healthy population of the UK [Dietary Reference Values (DRV) (DoH, 1991)]. When comparing nutrient intakes to the DRV, it is important to recognise that the latter are estimates of the needs of healthy population groups and not specific requirements for an individual. The DRV describe 3 levels of recommendations based on an assumed normal distribution of the population. The RNI's tend to be quoted for a majority of nutrients, representing an intake calculated to be sufficient to meet the requirements of 97.5% (mean + 2 SD) of the population. The EAR is used for recommendations regarding energy and represents the mean estimated energy requirement for the population. The Lower Reference Nutrient Intake (LRNI) is only likely to be sufficient for a minority of the population (2.5%) and thus if individuals habitually eat less than the LRNI for a nutrient, they will almost certainly be deficient in that nutrient. Despite its limitations, the RNI tends to be used in clinical practice as the goal for ensuring adequate provision of a nutrient for an individual. Less than 80% RNI is frequently used to indicate potential deficiency of that nutrient for an individual, a value often similar to that given by the EAR. Use of the LRNI to determine inadequate nutrient intake is not sensitive enough, as this would represent severe nutrient deficiencies for a number of children.

Sources of recommendations from different countries produce varying recommended intakes, in part due to the different adjustments adopted to allow for individual variations. An example of this is the differences seen between the FAO/WHO/UNU (1985) and American RDA (Committee on Dietary Allowances, Food and Nutrition Board, 1980) recommendations for protein, with the latter recommending 15-50% higher values at most ages, despite both recommendations being based on the same data. The FAO/WHO/UNU recommendations are based on reference proteins of higher biological value (such as those found in milk or egg) than those used for the RDA's and represent the minimal protein intake needed to sustain nitrogen balance in normal individuals. The RDA's are adjusted upward to allow the RDA to encompass the nutritional requirements of 95% of the healthy population, including consideration of

the lesser utilisation and digestibility of proteins from a typical American mixed diet of both animal and vegetable protein.

Based on current evidence (section 2.1), it was felt that the 3 day prospective semi-quantitative diet diary including a weekend day, as currently used in clinical practice and as recommended in the K/DOQI nutrition clinical practice guidelines (NKF-K/DOQI, 2000), would be appropriate for this study. Dietary intakes of all children were quantified at recruitment for baseline data, and subsequently reassessed at 1 and 2 years in those with a degree of renal failure. Changes in food and nutrient intake resulting from dietary intervention could thus be documented, noting whether there were any parts of the dietetic advice which were more readily adopted than others. It is acknowledged that the true accuracy of this method for assessing nutrient intakes of children with differing levels of CRI is questionable, particularly in relation to micronutrient intakes and conclusions should therefore be considered with caution. As a tool for comparison with severity of CRI however, it may be possible to highlight notable differences between groups. Energy, protein, fat and carbohydrate, sodium, calcium, phosphorus, iron, folate and vitamin C were identified as important nutrients for consideration in the dietary management of children with CRI (Table 1.4).

All parents and older children consenting to partake of the study were asked to complete a food diary at home at the time of recruitment, following advice provided on the day of the GFR by a dietitian on how to complete such a diary. The booklet included general questions such as the type of milk, bread and fats used, whether sugar and salt is added to food and whether any additional nutritional supplements are taken. Advice on completing the diary included providing labels of the nutrient composition of new manufactured foods, which could then be matched with a food of similar composition on the computer programme, quoting weights from packets where possible, listing manufacturers, using spoon measures for suitable foods (unstandardised), describing the method of cooking, and measuring the amount of undiluted cordial for squash, or milk for tea. Portion sizes could be described as small/ medium/ large and compared with standard portion sizes quoted by MAFF (1993), which have been incorporated into the Compeat-5 dietary analysis programme (Carlson Bengston Consultants Ltd, London, UK) for Microsoft Windows. The portion sizes are not specific to children however, so experience is required in interpreting them. In all children, with the exception of those

with 'normal' kidney function, a further diary was repeated at one and two years thereafter.

Nutrient intakes were calculated by one of two dietitians using the computer programme Compeat-5, the database of which is regularly updated, and based on the McCance and Widdowson composition of food tables, editions 4 and 5 (Paul & Southgate, 1978; Holland et al, 1991) and the Royal Society of Chemistry Nutrient Databank. Supplements to McCance and Widdowson food tables are also included in the software, the last of which was published in 1996, and hence the database had not changed during the analysis period of the study. The Compeat-5 programme provides comparison of the individual's nutrient intake with that recommended for the healthy UK population for age and sex (DoH, 1991).

Nutrients were compared against recommendations for chronological age rather than height age, as the preliminary and final 95% confidence interval (CI) data for baseline height SDS suggested that very few children in the study had a height below –2SDS (Tables 5.1.1-5.1.4; appendix 2). Energy was therefore described as a percentage of the EAR (with and without the addition of nutritional supplements), for which there are more comprehensive recommendations than for energy expressed as per kg body weight (DoH, 1991). Protein was expressed per kg actual body weight as most recommendations for children with CRI are expressed in this manner. Due to the importance of sufficient energy being available for effective protein utilisation, protein was also expressed as a percentage of total energy intake. Total fat, saturated, mono- and poly-unsaturated fats, total carbohydrate and total sugars were all expressed as a percentage of total energy intake. The computer database for fat type, especially unsaturated fats is incomplete and hence the subtotals of fat type do not equate to total fat intake. Analysis of fat type therefore has to be undertaken with extreme caution. Sodium intake was expressed both as a total and per kg actual body weight, total phosphate intake was reported in line with weight-related daily recommendations for total phosphate intake for children with CRI (Coleman, 2001), and calcium, iron, folate and vitamin C were expressed as a percentage of the RNI for chronological age. Micronutrient intakes represent dietary intakes only and exclude that obtained from the addition of micronutrient supplements.

As a small number of diaries were analysed by my colleague, it was necessary to check the reproducibility of results obtained by both observers. Six food diaries assessed by my colleague (JC) using Compeat-5 were subsequently assessed in the same manner by myself. Specific nutrients were compared by statistical correlation, and the minimum and maximum difference between the observers for each nutrient was calculated as a percentage of the mean difference (Table 3.4.1). These results suggest that the inter-observer variation was small and thus the method for estimation of nutritional intake from 3 day semi-quantitative food diaries was reproducible. The reproducibility of results was surprising, when compared to repeatability testing by others, as summarised by Bingham (1987), and this may reflect the close proximity in which my colleague and I work. Results from the food diary were relayed to the children and carers on the day of their clinic appointment if the diary was received in advance, or via telephone if the diary was received on the day of their appointment. This difference in feedback could impact upon the subsequent degree of concordance to advice, believing that the visual impact of seeing the results of their diary may have a greater impact.

Table 3.4.1 Correlation of inter-observer variation for estimation of food intake from 3 day food diaries

Nutrient	Patient no.	Energy (% EAR)	Protein (g/kg)	Protein (% Energy)	Total fat (% Energy)	Sugar (% Energy)	Sodium (mmol/kg)	Calcium (% RNI)	Phosphate (mg)	Iron (% RNI)
Analyst JC	1	112	1.4	10	34.3	24.5	2.1	89	1059	50
	2	126	2	9.3	34.8	30.2	3.9	94	1319	98
	3	98	1.7	11.5	33.9	20.1	4.3	73	1123	104
	4	105	1.5	10.8	43.1	17.6	3.6	80	1054	70
	5	113	2	10.4	29.6	22.3	4.2	74	1208	78
	6	98	2.3	11.5	34.6	24.8	6.9	190	1124	104
Analyst LN	1	122	1.4	9	32.9	24.6	2.2	83	1111	54
	2	124	1.7	8.4	32.6	31.7	4	91	1359	97
	3	93	1.5	10.7	30.5	24.1	3.8	68	1035	98
	4	108	1.5	10.5	44.8	18.1	3.5	76	1022	73
	5	110	1.9	10.3	27.7	22.8	4.2	74	1225	79
	6	95	2.2	10.8	34.8	33.4	6.9	191	1083	106
Correlation r =		0.91	0.94	0.94	0.98	0.82	0.99	0.99	0.92	0.99
Range of Difference (%)		2-9	0-15.8	0-10.5	0-10.6	0-29.6	0-12.3	0-7	1-8	1-8

3.4.2 Current practical dietary advice

Dietetics is concerned with the translation of nutritional theory into practice. The philosophy behind the practice in this unit is, that to achieve compliance to advice, it should be delivered in a concordant manner, personalising the advice according to each individual's likes and dislikes, whilst taking such factors as socio-economic status into account. Utilising strategies for improving adherence (section 1.3.9) has meant that the dietary goals have been achieved more readily in some children than others within the unit, depending upon the number of changes to each individual's eating pattern required. Paediatric renal diets are generally designed to be as liberal as possible, to achieve optimal growth and maximise adherence (Tamanaha et al, 1987). Restrictions are imposed only when there is a clear indication of need. From clinical experience, initial advice often involves sympathetic encouragement to anxious parents and attempts to discover the taste preferences of the individual child. Adopting and maintaining changes to eating habits is easier for a child if family members make similar changes, or at least avoid eating restricted foods in the child's presence. In the study unit, caregivers outside the family such as grandparents and school staff are made aware of dietary restrictions and asked to provide consistency of care in helping the child follow their diet (see appendix 4 for advice sheet for schools).

Dietary advice was provided to each child and family, in accordance with findings from their dietary assessment. Advice was given in an attempt to reduce the symptoms of uraemia, delay the progression of CRI, control hypertension and hyperlipidaemia, promote growth and prevent renal osteodystrophy and renal anaemia (Table 1.4). As a general measure, attempts were made to moderate protein, phosphate and salt intake and ensure an adequate energy and micronutrient intake in every child. The appendix contains dietary information that may be given to a child, depending upon the severity of renal failure, adequacy of appetite and dietary intake, growth and clinical condition. The advice sheet on phosphate restriction would usually be given as a priority, and information on energy, carbohydrate and fats would be given if attempting to either increase or reduce their energy intake. The protein information sheet would be provided if the child was seen to be eating large portions of meat or fish, having HBV protein sources more frequently than twice a day, and/ or if they exhibited a high plasma urea concentration in comparison to their plasma creatinine (no child was in receipt of a steroid which can falsely elevate plasma urea). Salt information was given if they were

not polyuric and/ or in need of sodium chloride or bicarbonate supplements, and finally information about foods rich in iron would be given if they were identified as having a low dietary iron intake.

At baseline, the results of the food diary were discussed with the child and family in all 4 groups. If possible, the discussion would occur face to face, at the time of their follow-up appointment in clinic to discuss the results of the GFR. If this were not possible, feedback would be provided via telephone. This is less satisfactory as the dietitian is unable to engage the younger child in the process. The dietitian would attempt to talk to the child if at all possible, and children as young as 4-5 years could be involved, even if this just helps to provide the parent with more power to initiate a change. This variable method of feedback could influence the ability of a child and family to adopt the recommendations, where one would perhaps expect that a face to face contact may be more successful in initiating a change in behaviour compared with a more indirect consultation. The majority of children and families however, did receive advice face to face, although unfortunately this data is not available.

The computer software allows the results to be expressed in various ways, which can then be printed out and shown to the family. The print-outs chosen involved a summary of intake, which represents the results diagrammatically, comparing their intake with that recommended for each nutrient for a child of the same age and sex. The figures for actual and recommended nutrient intakes can also be printed. Another useful output is that which produces a bar chart for daily energy intake, which enables one to compare the fluctuation in daily energy intake during the recording period. The final output used for the study concerned the proportion of foods contributing to each nutrient, which enables the dietitian to target those foods which have the greatest impact on the intake of each nutrient in question. This latter output, which describes each food as a percentage contribution to a nutrient, could be used to observe changes in food intake within children over the two year period.

Children with mild and moderate CRI were subsequently reviewed in clinic by a dietitian every 6 months, and those with severe CRI every 3 months. Children with mild CRI exhibited very few signs or symptoms of disease, and were therefore the more difficult group to provide positive feedback regarding the effects of any change made to

their diet on clinical or biochemical variables. The 3-6 monthly intervals between the yearly food diary assessments were used to identify any difficulties that they were having in following the dietary advice given, based on the previous food diary assessment, and to identify any foods that had since been substituted into the diet which should also be limited. It may be that those children, namely those with severe CRI, who were receiving more frequent medical and dietetic review were as a result, more able to achieve and maintain the dietary recommendations provided. Additionally, more emphasis seems to be placed by consultants on adopting dietary change in children with severe CRI, particularly compared with those with mild CRI, which could impact on the success of dietary intervention in mild CRI.

The remainder of this section outlines the dietary advice that is given to children within the study unit, based on best available evidence at the current time. Despite introduction of the DOQI nutrition guidelines in 2000, the recommendations have not needed to be modified and the advice remained consistent during the study period.

Energy (section 1.3.5 & 1.3.6; appendix 4 – carbohydrate and fats)

The initial aim is for an energy intake equal to the EAR for chronological age, unless height is below –2SDS, when height age should be used. Energy requirements are subsequently modified based on the individual's growth and weight gain. Increasing intakes of starchy foods are encouraged, along with the use of additional fats of the mono/ polyunsaturated type, substituting for saturated sources where possible [it is recommended that saturated fat forms < 11% of total energy intake and polyunsaturated fat forms between 6-10% of total energy intake (DoH, 1991)]. The addition of cakes, biscuits and puddings to the diet of a child who is not gaining weight satisfactorily is encouraged, regardless of fatty acid content. Addition of sugar (sucrose) to food and drinks is also currently promoted, in contrast to that recommended for the healthy population, where the aim is for sugars to provide a maximum of 10% of total energy intake (DoH, 1991). An energy supplement, usually a glucose polymer is often prescribed in addition for children with an energy intake below 80% EAR and/ or with poor weight gain. The impact of additional sugar/ carbohydrate and fats on serum lipids requires evaluation. Milk substitutes were not considered to be an energy supplement in this study, as they are primarily used as a direct substitution for cows milk, thereby maintaining energy intake rather than supplementing it. In overweight children with

mild CRI where hypertension is the main concern, advice is likely to be given to reduce energy intake, via substitution of high-energy snacks with fruit and use of sugar free drinks.

Protein, phosphate & calcium (sections 1.3.4 & 1.3.7; appendix 4 - protein & phosphate)

Dairy products are restricted, usually to 150-200ml milk/day, yogurts, cheese, eggs and chocolate to twice a week, and other foods notably high in phosphate should be avoided such as nuts and carbonated drinks preserved with phosphoric acid e.g. cola. Low protein milk substitutes are prescribed for children who were previously 'big milk drinkers' or for use in home-cooked milk puddings. Obtaining 100% RNI for calcium is encouraged within the weight-related range of phosphate restriction [400-1000 mg/d phosphate (Coleman, 2001)]. A target phosphate intake of < 1000mg/d was used for assessing the study cohort, as this was the appropriate goal for the majority of children. A calcium supplement is considered in children achieving < 80% RNI for calcium, but is currently rarely instigated. There is a tendency to increase dairy products where phosphate intake is low to improve calcium intake, rather than keeping dietary phosphate to a minimum with prescription of a calcium supplement. High biological value sources of protein are restricted to a 'small amount' (approximately 60g) twice a day, in an attempt to bring the child's traditionally high protein intake closer to 100% RNI for protein, which for children above 1 year of age is equivalent to 1-1.1 g/kg. This recommendation tends not to be strictly enforced in children where it is difficult to achieve adequate energy intakes. Generally, a reduced protein diet for children would be represented by intakes of between 0.8-1.2 g/kg/d. Low biological value sources of protein such as bread and other starchy foods are not restricted, due to their importance as sources of energy. Low protein specialised products are not encouraged as alternatives, due to this resulting in segregation of the child from their peers and family.

Salt (section 1.3.2; appendix 4 – salt)

A salt (sodium) restriction known as a 'No Added Salt' diet, equivalent to 80-100 mmol sodium/ day is advised for the majority of children. This involves avoiding adding salt to food at the table, using a small amount in cooking and limiting foods high in salt which have little nutritional value, such as soups, pot savouries, sauces and gravies and controlling the amount of crisps and other salty snacks eaten. Ham and cheese (limited

by phosphate restriction) are allowed as part of a varied diet as they are foods commonly preferred by children. The use of tinned products should be limited by ensuring that they are interspersed with the use of fresh foods, and lower salt varieties encouraged where possible. The exception to NAS advice being administered is for children who are prescribed sodium chloride or sodium bicarbonate, due to polyuria and salt-wasting, or in relation to metabolic acidosis. In these instances however, reduction of salt intake is likely to be necessary in the future, and therefore basic advice and education may still be given if it was felt to be appropriate.

Vitamins and iron (section 1.3.8; appendix 4 – iron)

Advice on good food sources of vitamins and iron is provided, encouraging the daily intake of breakfast cereals fortified with vitamins and iron, accompanied by a good source of vitamin C to promote the absorption of non-haem iron. Red meat is encouraged as a rich source of the more readily absorbable haem iron. Fruits and vegetable are encouraged in those children who are willing to consume them, and vitamin C rich drinks are recommended such as orange juice in those with mild CRI and blackcurrant squash in those with more severe CRI, where avoidance of high potassium foods may be an issue. The aim is to achieve 100% RNI for vitamin and iron intakes, and a water soluble vitamin preparation; Ketovite tablets (Paines & Byrne, West Byfleet, UK), and/ or an iron preparation is prescribed in those children failing to achieve 80% RNI.

3.4.3 Assessment of anthropometry and blood pressure

Anthropometry

For the purpose of this study, weight, height and MUAC were measured and BMI calculated, as described in section 2.2. Weight, height, BMI and MUAC were recorded at recruitment and at 6-monthly intervals thereafter, to determine whether growth improved, was maintained or deteriorated over the two year period. Weight and height were measured on the ward at recruitment, and subsequent measures were obtained at the outpatient clinic, by clinic staff trained by an auxologist. Comparisons were observed between the height obtained on the ward and the next nearest height measurement obtained in outpatient clinic, whether it be prior to recruitment or

subsequently, to ensure reproducibility of results (Table 3.4.3.1). Following analysis, it was recognised that a number of children were being grossly misclassified for height by the ward stadiometer. On investigation, it was found that the stadiometer was faulty and the part was replaced. Height measurements on the ward subsequently were in keeping with those obtained in clinic. For those children who were misclassified, the nearest clinic height to that obtained at recruitment on the ward was used instead. This was only necessary for a total of five patients.

MUAC was measured by the dietitian most involved in the care of that particular patient (LN was responsible for all children with the exception of approximately 50% of the severe group). MUAC measurements were compared to centile tables (Frisancho, 1974). To ensure reproducibility of our measurements, both observers obtained a measure of MUAC on the same day, on a small sample of patients (n=12), findings were correlated and also compared for centile misclassification (Table 3.4.3.2). Measurements by both observers in all but one child corresponded to the same centile, despite JC having a tendency to round the value to the nearest 0.5cm. The one discordance was likely to be due to the confusion concerning the identification of the non-dominant arm, as the mother of this deaf child was not available to clarify the matter with one of the observers. The values were either average or below average for age which is not surprising as these were all obtained from children with severe CRI. These findings support the reproducibility of MUAC being obtained by either observer.

Blood pressure

Hypertension is commonly associated with CRI and thus blood pressure should be measured in every child, particularly as lowering blood pressure has been shown to reduce the progression of CRI (section 1.3.1). The British Hypertension Society provides guidelines as to how to measure blood pressure (Ramsay et al, 1999). The device should be properly maintained and calibrated. The patient should be seated with the arm at the level of the heart. The bladder size should be adjusted for arm circumference, the cuff deflated at 2mm/ second and blood pressure measured to the nearest 2 mm Hg. Diastolic pressure is recorded as disappearance of the sounds (phase V). At least two measurements should be made at each of several visits to determine blood pressure thresholds. Ambulatory blood pressure monitoring can be helpful, particularly in children where they are often suggested to exhibit 'white coat

hypertension', denoted by a falsely elevated SBP. In adults, optimal blood pressure treatment targets are a SBP < 140 mm Hg and a DBP < 85 mm Hg. In children, centiles are required, as blood pressure increases with age, growth and development (de Man et al, 1991). The 7 centiles (5^{th} – 95^{th} centile) are related to height, and commence at a height of 100cm in boys and 95cm in girls. The goals for children are to maintain both systolic and diastolic blood pressure readings below the 95^{th} centile (within 2 standard deviations) for normal children of the same height and sex.

Standard deviation scores

Standard deviation scores were calculated for weight, height, BMI, MUAC and BP. SDS's were not calculated for height velocity due to the age spread, including a significant number of pubertal children for whom it would not be appropriate. For MUAC and BP, SDS's were obtained by converting discreet tabled percentiles (Frisancho et al, 1974 and de Man et al, 1991 respectively) into a corresponding z score (standard Normal deviate) obtained from the Normal distribution tables, resulting in discreet SDS data for MUAC and BP. SDS's for weight and height could be calculated from either the revised Castlemead Growth Programme based on the revised Tanner & Buckler data (1997) or the Child Growth Foundation Microsoft Excel macro, based on the UK 90 data (Freeman et al, 1995). Our data showed good correlation between the two for both weight (r=0.985) and height (r=0.989).

Bland and Altman plots (1986) for SDS's derived from the two reference data sets for height and weight, as depicted in Figures 3.4.3.1 and 3.4.3.2 respectively, suggest that for height, the majority of data using the Child Growth Foundation norms gave SDS values 0 to 0.4 SDS lower than the Castlemead data, with a mean discrepancy of –0.283 SDS. For weight, the mean discrepancy of –0.123 SDS was closer to zero, with the differences ranging from 0.6 to –0.7. The mean SDS values for height and weight for children with 'normal' renal function at recruitment were 0.19 ± 1.02 and 0.28 ± 1.01 respectively using the Child Growth Foundation data and 0.48 ± 1 and 0.4 ± 1.05 respectively for the Castlemead growth programme. SDS values close to zero would be expected in a group of children considered to be representative of the healthy population. In discordance with the RCPCH (2000) report, a discrepancy between the revised Tanner & Buckler data (1997) and UK 90 data for both weight and particularly height were observed, which was expected for weight, but not height. This brings into

question the validity of the revised Castlemead Growth Programme, which requires future examination. In the meantime, weight, height and BMI were converted to SDS using the Child Growth Foundation data (Freeman et al, 1995), which was felt to be more representative of the current population.

Table 3.4.3.1 Comparisons between clinic and ward heights

Patient	Ward height (cm)	Clinic height (cm)	[a]Time (wks) Difference	Ward centile	Clinic centile
1	103.6	103.6	6	1	1
2	104.7	105.6	4	6	7
3	98	97	4	5	3
4	119	118.7	3	5	4
5	160	159.4	6	36	33
6	124.2	123.4	1	18	14
7	136	136.9	3	11	12
8	117.3	113.8	6	19	7*
9	139	139.1	3	4	4
10	147.1	147.5	4 prior	95	96
11	135.6	136.7	8	4	5
12	154.8	154.2	8 prior	12	11
13	133	133.3	7	89	87
14	95.1	97.1	3	50	66*
15	83.6	83.9	4	12	12
16	132	132.7	4	2	2
17	149.8	150.1	5	12	12
18	167.9	163.4	28	85	58*
19	113.6	109.3	4	86	57*
20	122.5	132.1	4	6	53*

Key: [a]Time difference is denoted as clinic heights being subsequent to ward heights unless otherwise stated.

*Clinic heights in these cases were used in place of the ward height

Table 3.4.3.2 Comparison of inter-observer variation in measuring mid upper arm circumference (MUAC)

Patient	MUAC (cm) [a]LN	JC	Difference (cm)	[b]MUAC SDS LN	JC
1	20.8	20.9	-0.1	-2	-2
2	16.9	17	-0.1	-0.67	-0.67
3	21.3	21	+0.3	-0.67	-0.67
4	18.4	18.5	-0.1	0	0
5	18.8	19	-0.2	-0.67	-0.67
6	17.8	17.5	+0.3	0	0
7	20	20	0	-0.67	-0.67
8	18.5	18.5	0	-0.67	-0.67
9	15.8	15.8	0	-0.67	-0.67
10	21	20.6	+0.4	-2	-2
11	17.2	16.6	+0.6	-0.67	-0.67
12	22.2	21.5	+0.7	-0.67	-1.28 *
Correlation r =	0.99			0.97	

Key: [a] Observers

[b] Discrete SDS scores

* The value obtained by the usual observer (JC) was used

Figure 3.4.3.1 Bland & Altman plot for comparison of height SDS as calculated by Castlemead Data (C) and Child Growth Foundation Data (CGF)

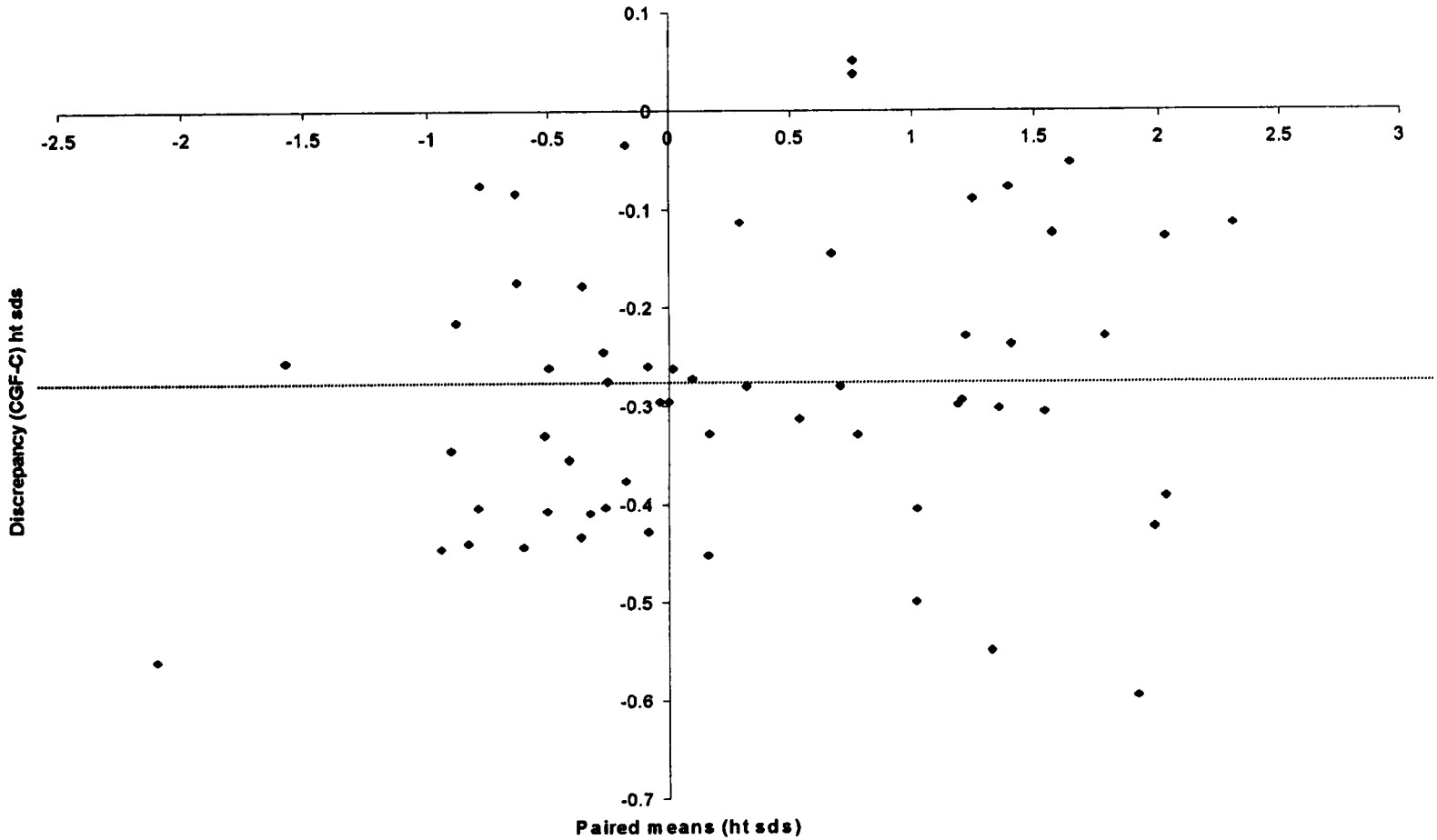
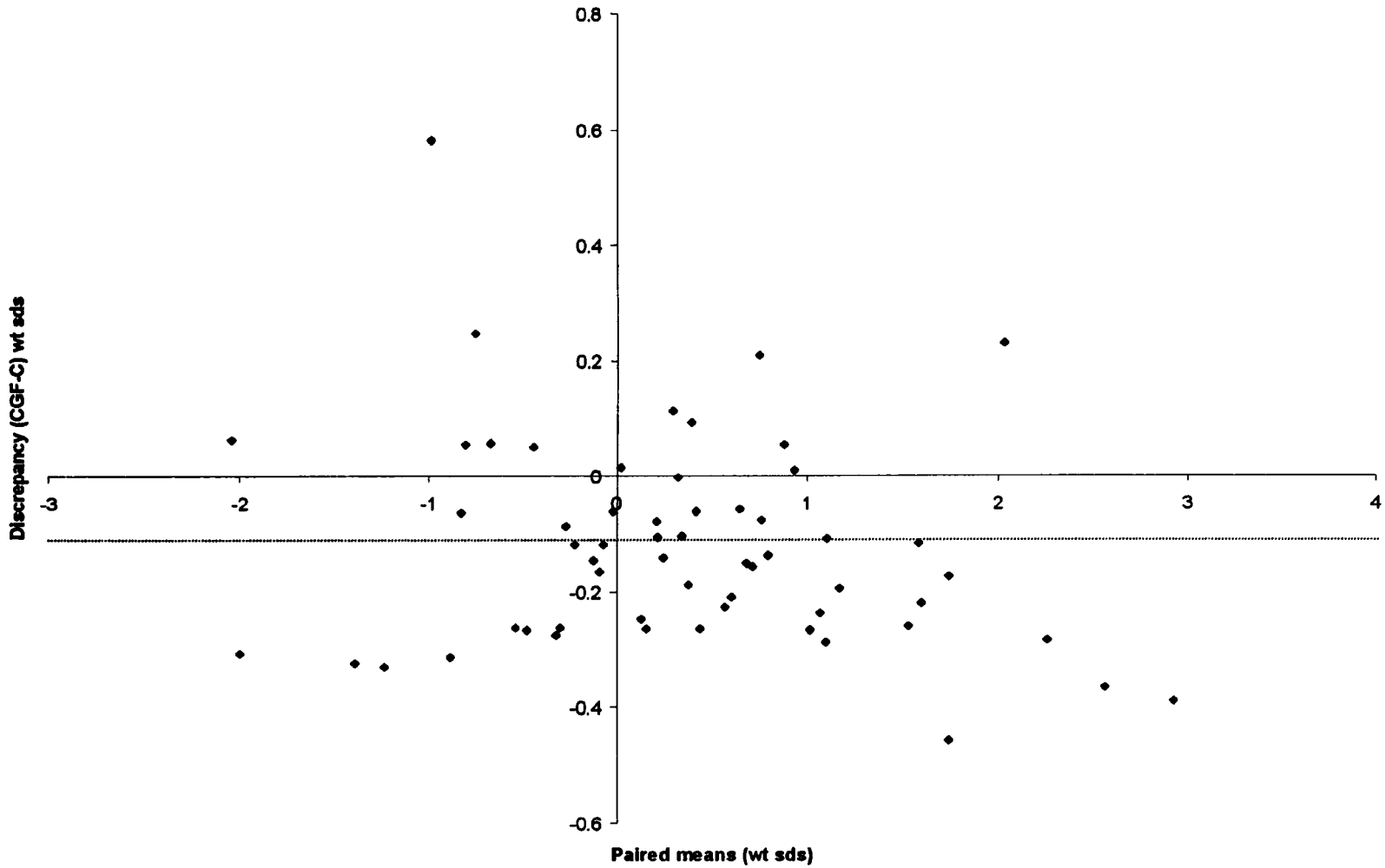


Figure 3.4.3.2 Bland & Altman plot for comparison of weight SDS as calculated by Castlemead Data (C) and Child Growth Foundation Data (CGF)



3.4.4 Assessment of biochemical status

All biochemical variables were obtained at recruitment and at 6 monthly intervals over the 2-year period. Serum albumin and prealbumin were measured as markers of nutritional status, and serum lipids were monitored to observe any effects resulting from recommendations to increase fats and sugars and/or change fat type. The management of renal anaemia was guided by haemoglobin, plasma ferritin concentrations and percentage hypochromic cells, and serum PTH, calcium, phosphate and alkaline phosphatase were used as indicators for the management of renal osteodystrophy. Urine and electrolytes were also obtained as part of normal clinical practice.

Urea and electrolytes

Plasma urea and electrolytes are monitored as part of routine clinical practice and plasma sodium, potassium, urea and creatinine concentrations are detailed. Dietary potassium restriction is not discussed in this thesis as it is only usually required in children with CRI once they approach ESRD. Children with nephritis or those on potassium-sparing medications may require earlier intervention. Plasma bicarbonate is routinely measured as a means of monitoring acid-base balance, where metabolic acidosis is often detected in those with more severe CRI and among other things has been associated with poor growth, anorexia and bone malformation (Hanna et al, 1991). Sodium bicarbonate is administered to children who routinely exhibit plasma bicarbonate levels under 18 mmol/l (Tables 3.3.5-3.3.7). Plasma levels and medical treatment are thus addressed, but are outside the scope of this thesis due to the limited role of diet in its prevention.

Bone-related variables

Plasma levels of phosphate, calcium, alkaline phosphatase and PTH are routinely measured in renal units, due to the risk of developing renal osteodystrophy if undertreated, or adynamic bone disease or hypercalcaemia if overtreated (section 1.3.7). It is important that plasma phosphate concentrations are compared to the age appropriate reference range.

Plasma phosphate age-related laboratory reference range

Age	Plasma phosphate concentration (mmol/l)	Age	Plasma phosphate concentration (mmol/l)
< 4 wks	1.2 – 3.1	3-6 years	1.0 – 1.8
5 wks – 6 months	1.5 – 2.4	6-15 years	1.0 – 1.7
6 months – 1 year	1.5 – 2.1	Adult	0.8 – 1.4
1-3 years	1.2 – 2.0		

For the purpose of this study, the reference range that applied to the largest proportion of the study population was used (1-1.7 mmol/l). Levels of PTH fragments may be raised in individuals with poor renal function, due to impaired excretion rather than secondary hyperparathyroidism (Hruska et al, 1977). The measurement of intact, biologically active molecules avoids this problem. Jureidini et al (1990) compared plasma PTH levels analysed by both methods and found elevated levels of PTH mid-molecular fragments in the plasma. Serum intact PTH is routinely measured by our laboratory, with a normal reference range of 12-72 ng/l.

Anaemia-related variables

Full blood count, serum ferritin which is a measure of iron stores, and percentage hypochromic red cells; a marker of iron availability, were obtained at 6 monthly intervals to identify children with renal anaemia, in line with the unit's current clinical practice.

Plasma proteins

Total serum protein and/ or albumin is suggested to be the most useful of the plasma proteins for assessment of nutritional status in children with CRI, although different methods of analysis produce different results (section 2.3). For the purpose of this study, being only one of two hospitals in the UK at the time of commencing the study to use the BCP rather than BCG method for analysis of plasma albumin, a comparison between the BCP method and a 'gold standard' was made. The gold standard for this study involved using an immunoturbidometric assay (ITM), performed on a Cobas Fara Analyser (Roche Diagnostics Ltd, East Sussex). Six monthly samples were routinely analysed by the BCP method, and stored plasma was used to batch analyse by the ITM

method. The aim was to determine whether, like Wells et al (1985), a difference in plasma albumin values could be observed between the groups of children with differing levels of CRI.

Plasma prealbumin has been proposed to be an independent marker of nutritional status in adults on haemodialysis (Avram et al, 1995). Little has been published regarding prealbumin concentrations in children however, with or without CRI. Due to the current lack of evidence available, plasma prealbumin was assessed in this study, also using a turbidimetric method on the Cobas Fara Analyser from stored plasma, to establish plasma concentrations of prealbumin in a group of children of different ages and varying levels of renal failure.

Measure of proteinuria

Protein:creatinine ratio in spot morning urine samples has been demonstrated to be a precise indicator of proteinuria and reliable predictor of progression in adults, and is much easier to perform than a 24 hour urinary protein collection (Ruggenenti et al, 1998b). The higher the ratio, the faster the decline in GFR. Adult patients with a ratio of <1.7 had the lowest rate of glomerular decline whereas patients with a ratio of >2.7 lost more than 10ml/min/1.73m^2 of filtration rate per year. The protein: creatinine ratio from spot morning urine samples is the method of choice in the study unit, and it was measured in all children at each 6 monthly clinic visit in an attempt to compare this with the rate of progression of CRI. Only 2 children at baseline had a protein: creatinine ratio of > 1.0 g/l and no child exhibited a value above 1.7 g/l. The range of protein: creatinine ratios to categorise differing levels of proteinuria in this study were therefore not comparable to that found in adults as described above (Ruggenenti et al, 1998b). Attempts were made to identify those children with substantial proteinuria associated with suboptimal plasma albumin concentrations, so that other biochemical variables that are influenced by low plasma albumin concentrations, such as serum lipids, could be accounted for. 14% of all children had a plasma albumin concentration $\leq$ 35 g/l. By using frequencies, the protein: creatinine ratio cut-off for the upper quintile was chosen. 21% of the study population had a ratio of $\geq$ 0.1g/ mmol, of which 46% had a plasma albumin concentration $\leq$ 35 g/ l. This value captured the greatest proportion of children with a low albumin. A protein: creatinine ratio of 0.1g/mmol (normal < 0.02 g/ mmol)

was therefore used to indicate a substantial degree of proteinuria in the study population.

Serum lipids

Non-fasting lipids were monitored in this study for total serum cholesterol, HDL cholesterol and triglyceride concentrations to ascertain the impact of recommending a change in fat type or increase in the use of sugars. It is not current practice to ask for fasting samples in children that could be as young as two years of age, although a fast of four hours as previously suggested may have been acceptable (Kari et al, 1998). Total cholesterol concentration is unaffected by a meal, although a recent illness, infection or surgery can reduce total cholesterol, as can a long-term deficit in energy intake. Serum triglyceride concentrations however increase substantially following a meal, preventing reliable interpretations of changes in serum triglyceride concentrations during the study period. The goals for lipids would be that fasting triglyceride concentrations are below 2 mmol/l and HDL cholesterol above 1 mmol/l (section 1.3.6). LDL cholesterol was calculated according to the following equation:

LDL = Total cholesterol – HDL – Triglyceride/ 2.2

This equation, which includes the concentration of triglyceride could therefore produce artificially lower serum LDL concentrations than might be obtained if a fasting sample was taken. The serum triglyceride concentration also needs to be under 4.5 mmol/ l for this equation to be valid. Estimated LDL concentration however, was successfully obtained in the majority of children throughout the study, despite their unfasted state. It was likely to have been at least 2 hours since the child's last meal, with many families having quite large distances to travel to the unit and on arrival, the child is usually faced with a wait before the blood test is taken.

3.5 Summary of study protocol (Table 3.5)

	Time (months)				
	0	6	12	18	24
GFR – (^{51}Cr EDTA)	✓				
Estimated GFR_{creat}	✓	✓	✓	✓	✓
Estimated $GFR_{cys\ C}$	✓	✓	✓	✓	✓
Dietary analysis – 3 day semi-quantitative food diary	✓		✓		✓
Anthropometry – Weight, height, BMI, MUAC	✓	✓	✓	✓	✓
Biochemistry – Serum U&E's, Bone parameters, FBC, ferritin, % hypochromic cells, albumin, prealbumin, lipids, urine protein:creatinine	✓	✓	✓	✓	✓
Dietary adherence & advice	✓	✓	✓	✓	✓

NB. Children with a GFR > 75 ml/min/1.73m^2 provided baseline (0 months) data only.

3.6 Statistics

Data were analysed at baseline for comparison between the 4 groups; 'normal', mild moderate and severe CRI. Descriptive anthropometric data were presented as mean, SD and 95% CI, being deemed to be normally distributed. Due to a combination of normal and skewed data for the various nutritional indices and biochemical variables, non-parametric descriptives were used (median and interquartile range), which help to describe the magnitude of skewness more clearly than the mean and standard deviation.

One-way analysis of variance (ANOVA) was calculated for normally distributed continuous data, incorporating the least significant difference (LSD) post hoc test and 95% CI of the difference. Despite BP SDS exhibiting a high level of skewness, the data were discreet, with a large number of ranked ties rendering the non-parametric test unsuitable for comparison between groups. In this instance, one-way ANOVA was used with LSD post hoc test. For other data, the two sample Mann-Whitney U-test was used. The relationship between GFR and a number of variables was evaluated by simple linear regression analysis. Partial correlation coefficients were used to observe whether correlation existed between variables, once GFR was controlled for. The level of significance was set at a probability of less than 5% ($p<0.05$). All calculations were done using the computer package SPSS-9 for Microsoft windows, 1999.

Statistics used in the estimation of GFR are described in chapter 4. The two year data were analysed using a general linear, univariate analysis of variance (UNIANOVA) model. A general linear model involves calculating the best fit for changes in each variable over time and comparing it to baseline values. Syntax had to be written to enable different errors to be included for each part of the model. The model was written to describe the following:

Group - to describe differences between the groups

Visitno - signifies change over time, with observations being made at 6 monthly intervals

*Group*Visitno* - signifies differences in change between the groups over time

Group(id) - to describe differences between individuals within each group

Visitno(id) - to describe differences between individuals at each visit

The syntax was written based on the *dependent variable*, referring to the calculated change in the variable between baseline and each visit number (6 monthly visits), a *fixed factor* (group), a *random factor* (patient id) and a *covariate* (visit number) (Figure 3.6 a & b). Change in a variable at each visit number compared to baseline was also calculated using syntax, in a two step process using height SDS as an example (Figure 3.6 c). In most instances, only *Visitno* was illustrated, which is the measure of significance of whether any changes in a variable were observed over the 2 year period for the cohort as a whole, and for the groups of CRI.

The relationship between the change in two variables over time was evaluated by forced stepwise linear regression, where the effect of time was accounted for (block one) before observing any additional effect attributed to the independent variable in question (block two). Longitudinal data analysed in this way will therefore have 2 degrees of freedom for the regression model. All baseline data were excluded, due to comparisons being made for changes in a variable compared to baseline.

Change in actual food intake over the two year period was evaluated more descriptively, by observing the percentage contribution that foods made to certain nutrients for each individual at baseline, one and two years. Foods that formed either the greatest or second greatest contribution to overall intake for a nutrient were described as a proportion of total nutrient intake (%), and means for both the greatest and second greatest contributions were obtained. The proportion of children consuming these most commonly eaten foods was also documented.

Figure 3.6 Statistical analysis using syntax for SPSS

a) UNIANOVA for the whole group

```
UNIANOVA  chtsds  BY group id WITH visitno
 /random = id
 /METHOD = SSTYPE(1)
 /INTERCEPT = INCLUDE
 /CRITERIA = ALPHA(.05)
 /DESIGN = group visitno group*visitno group(id) visitno(id) .
```

b) UNIANOVA for each group of CRI

```
UNIANOVA chtsds  BY id  WITH visitno
 /METHOD = SSTYPE(1)
 /INTERCEPT = INCLUDE
 /CRITERIA = ALPHA(.05)
 /DESIGN = visitno id .
```

c) Calculating change over time for each individual for a variable (2 step procedure)

```
/* Spread the htsds measurement from vistno=0 to subsequent visits to be used as a
baseline measurement

do if visitno=0.
 Compute bashtsds=htsds.
Else.
 Compute bashtsds=lag(bashtsds).
End if.
Execute.


/* Subtract the baseline measure from the subsequent measures of htsds.

Compute chtsds=htsds-bashtsds.
Execute.
```

Chapter Four

ESTIMATION OF GLOMERULAR FILTRATION RATE

4.1 Introduction

Glomerular filtration is the filtration of substances from the blood into the urine within the glomerulus of the kidney. Measurement of GFR is used as the main indicator of renal function, the knowledge of which may not only facilitate the safer prescribing of fluids, electrolytes and drugs, but also indicate the need for referral to a dietitian. GFR is defined as the clearance of a substance carried in the plasma that is not metabolised outside the kidney, and that is filtered freely across the glomerular membrane. The substance used for measurement of GFR should not be taken up or secreted by, or metabolised in, the renal tubules and urinary tract. Although urinary inulin clearance is the 'gold standard' for the measurement of GFR, measuring inulin is problematic. The test is inconvenient, as a constant infusion of inulin for a prolonged period to obtain a steady state is necessary, and accurate, timed urinary collections and sequential blood tests are required. Formal GFR estimation for this study involved the more easily measured plasma clearance of radio-labelled chromium-edetic acid (^{51}Cr-EDTA) as described by Chantler and Barratt (1972), which can be carried out as a day case.

In clinical practice, simple, non-invasive methods are required to routinely estimate GFR, although the limitations of these methods for estimation of GFR have been documented for both children (Hellerstein et al, 1988) and adults (Levey et al, 1988). The 24 hour creatinine clearance is widely used to estimate GFR, but difficulties in the accurate collection of timed urine samples, particularly from children, limit its value, and even under research conditions its reproducibility is poor (Chantler and Barratt, 1972). Creatinine is a physiologically inert substance that is normally only excreted by the kidneys. Creatinine however, is not only freely filtered by the glomerulus but is also secreted by the renal tubular cells and hence, creatinine clearance exceeds measured GFR. Creatinine and its precursors may be ingested in the diet and thus alter the rate of

addition of creatinine to body fluids (Bleiler & Schedl, 1962). Heavy exercise and pyrexia also increase the daily excretion of creatinine. There is an inverse relationship between GFR and tubular secretion of creatinine, so the ratio between creatinine clearance and measured GFR is greater at lower levels of glomerular filtration.

Despite the disadvantages of estimation of GFR from urinary and plasma creatinine, simple calculations have been derived in both adults and children which prove to be clinically useful, non-invasive tools for providing a rough estimate of the change in GFR over time. Creatinine excretion is relatively constant and therefore an inverse relationship exists between GFR and plasma creatinine concentrations, as depicted by the formula for estimation of GFR in adults, taking age, gender and body weight into consideration (Cockcroft and Gault, 1976):

[140 – age (yr)] x weight (kg) / 0.825 x serum creatinine (μmol/l)

(for women, multiply clearance by 0.85).

In healthy children, plasma creatinine rises with age, whereas GFR, corrected for body surface area, does not alter after the age of 2 years. GFR was subsequently determined to be proportional to body height and inversely proportional to plasma creatinine, and is frequently estimated in clinical practice using the equation derived by Schwartz and colleagues (1976) for children where:

GFR = K x height (cm)/ pCr

(K is a proportionality constant which is a function of the rate of urinary creatinine excretion per $1.73m^2$ and pCr is plasma or serum creatinine concentration).

Schwartz et al (1976) determined the value of K to be 0.55 if pCr is measured in mg/dl. If adapted for SI units, the proportionality constant would equal 48 [creatinine (mg/dl) x 88.4 = creatinine (μmol/l) i.e. molecular weight creatinine = 113]. Schwartz and colleagues (1987) extended their observations from low birth weight (LBW) babies through to adulthood. They noted that K was directly proportional to the muscle component of body weight and quoted K values of 0.33 for LBW babies, 0.45 for full term infants up to 1 year age, 0.55 from 2 years of age through adolescence in girls and 0.7 during adolescence in boys. Malnutrition resulted in lower K values, as did obesity where muscle mass is relatively smaller than in those of average weight.

Also in 1976, Counahan and colleagues published work regarding estimation of GFR from plasma creatinine concentration, for which the formula in SI units is:

GFR = height (cm) x 38/ plasma creatinine (μmol/l),

for children between 2 months –14 years age. The K value is considerably less than that quoted by Schwartz and was derived from plasma clearance of ^{51}Cr-EDTA rather than plasma creatinine clearance. Creatinine clearance will result in constant overestimation of GFR due to tubular secretion of creatinine. Hellerstein et al (1992) also proposed lower K values of 0.45 (40 in SI units) for girls and prepubescent boys and 0.57 (50 in SI units) for adolescent boys, despite using creatinine clearance to estimate the K value. They attributed their differences in proportionality constant values (compared to Schwartz et al (1976)), to the methods employed to measure urinary creatinine, and ideally recommend that K should be determined in one's own laboratory before applying it as a screening tool. The study unit tend to use a K value of 40, in part due to ease of calculation in the clinical setting.

Cystatin C was proposed as a marker of GFR 16 years ago (Simonsen et al, 1985). Unlike creatinine, cystatin C is a low molecular weight cysteine protease inhibitor, which is produced at a constant rate by all nucleated cells. Elimination is almost exclusively by glomerular filtration, and subsequently filtered cystatin C is reabsorbed and catabolised completely in proximal tubular cells (Tenstad et al, 1996). Inflammation and malignancy have no effect on its serum concentration. Studies in adults have shown cystatin C to be a more sensitive marker of changes in GFR than serum creatinine, with a normal reference range of 0.61-1.21 mg/l (Kyhse-Andersen et al, 1994) or a cut-off concentration of 1.25 mg/l for a GFR below 72 ml/min/1.73m^2 (Newman et al, 1995). Reference values of 0.63-1.33 mg/l (Helin et al, 1998) and 0.7-1.38 mg/l (Bokenkamp et al, 1998a) have been obtained for children over one year of age which, unlike creatinine clearance is of a similar order to that described for adults. Finney et al (2000) calculated 3 paediatric ranges: premature infants, 0.43-2.77 mg/l; under 1 year, 0.59-1.97 mg/l; and 1-17 years, 0.5-1.27 mg/l. In premature infants, cystatin C is significantly raised and reaches adult levels by the age of 1 year, which suggests it takes 12 months for the kidneys to attain maturity. Creatinine concentrations however, are influenced by increasing muscle mass during growth, not reaching adult values until after puberty, and subsequently do not reflect maturation of the kidney.

Detection of mild CRI is important to facilitate early medical and nutritional intervention in an attempt to delay progression, and maximise growth, nutritional and biochemical status (Norman et al, 2000). Regular, accurate assessment of renal function is required to ensure timely management appropriate for the stage of the disease. As serum cystatin C concentration has been suggested to be a more accurate marker of GFR than plasma creatinine, the measurement of cystatin C was incorporated into the study. The aim was to determine whether cystatin C was a better marker of GFR than creatinine/ height in screening for early renal impairment in children. It is also important to establish the validity of serum cystatin C in comparison to plasma creatinine/ height for measuring subsequent progression of CRI, longitudinal data for which has not yet been reported. As a result, it was felt to be useful to compare the values obtained for serum cystatin C with plasma creatinine/ height over the 2 year period. It is acknowledged however, that serum cystatin C concentrations subsequent to baseline could not be validated as a marker of progression of GFR, due to the absence of a gold standard measurement of GFR for comparison.

4.2 Methods and statistics

Plasma clearance of a radio-labelled substance is accepted as the 'gold standard' for measuring GFR and thus quantifying the level of kidney function. ^{51}Cr-EDTA GFR tests are carried out as a day case in the unit under study when deemed to be necessary, and used as the 'gold standard'. In routine clinical practice, the indirect, non-invasive method of estimation of GFR from plasma creatinine and height is utilised, as first described by Schwartz et al (1976) and Counahan et al (1976). Due to ease of calculation, the proportionality constant (K) of 40 is used in the study unit, such that the equation for estimating GFR is:

height (cm) x 40 / plasma creatinine (μmol/l).

An alternative indirect method has recently been suggested, involving a simple blood test for serum cystatin C concentration (Kyhse-Andersen et al, 1994; Newman et al, 1995). As storage time proved to have no systematic effect on cystatin C measurements (Bokenkamp et al, 1998b), retrospective analysis on the units' stored serum samples taken at the time of the EDTA GFR for cystatin C concentrations could be conducted and compared to creatinine/ height, with the EDTA GFR used as the reference for actual GFR.

Measurement of plasma clearance of ^{51}Cr-EDTA is not subject to tubular secretion or extra-renal uptake, and consequently plasma clearance is equivalent to GFR (Chantler & Barratt, 1972). EDTA plasma clearance gives a bi-exponential curve. The first reflects equilibrium between the intra-vascular and extra-vascular space and the second, clearance through the kidney. The first exponential can be ignored if blood sampling is carried out at least an hour and a half after injection of EDTA. In children, 5ml blood samples are taken 2, 3 and 4 hours after injection of EDTA. Results are compared with an age, sex and body surface area ($1.73m^2$) corrected normal range. Surface area was derived from height and weight, using the formula of Du Bois and Du Bois (1916):

$$BSA\ (m^2) = 0.007184 \times weight\ (kg)^{0.425} \times height\ (cm)^{0.725}$$

Body surface area can more simply be calculated by the equation:

$$\sqrt{[(height\ (cm) \times weight\ (kg))/ 3600]}$$ or estimated using a nomogram.

Play preparation has an important role in the study unit, and the child and family were sent a booklet entitled 'Graham has a GFR test', along with their appointment letter. This booklet is written as a children's story to explain the events as they will occur and thus familiarise the family and child with the procedure, in the hope of reducing tension and promoting co-operation on the day. Often an anaesthetic cream is used prior to insertion of needles in children and distraction techniques are utilised by nursery nurses in the treatment room during procedures.

Plasma creatinine concentrations were measured in our hospital using a modification of the Jaffé method (O'Leary method), performed on the Olympus AU600 (Southall, Middlesex). Serum cystatin C concentrations were measured using latex particle enhanced nephelometric immunoassays (PENIA) performed on the Behring Nephelometer Analyser (Dade Behring Marburg GmbH, Marburg, Germany) (Erlandsen et al, 1999) at the department of clinical biochemistry, St Bartholomew's and The Royal London School of Medicine and Dentistry, London, through joint collaboration with Professor Chris Price.

Statistics

The between batch coefficients of variation of the quality controls (QC) for each method were as follows: Jaffé creatinine (μmol/l), medium QC 1.6% (n=18, mean 100), high QC 0.65% (n=17, mean 480); cystatin C (mg/l), low QC 3.6% (n=10, mean 0.98), medium QC 4.2% (n=10, mean 2.58), high QC 4.4% (n=10, mean 6.49).

Simple linear regression was undertaken to determine correlation between both serum cystatin C and plasma creatinine with EDTA GFR, and to derive models for calculating GFR from these endogenous markers. Diagnostic statistics were used to compare the two indirect markers for estimating GFR with the gold standard EDTA method. Sensitivity (proportion of positives that are correctly identified by the test) and specificity (proportion of negatives that are correctly identified by the test) for each test were evaluated using receiver operating characteristic (ROC) curves (Zweig & Campbell, 1993). ROC curves are graphical representation of sensitivity (true positives, y-axis) plotted against 1- specificity (false negatives, x-axis) and co-ordinates of these curves are also given. For 100% specificity, the curve follows the y-axis. If the 'cost' of a false negative result is the same as that of a false positive result, the optimum ROC point is that which maximises the sum of the sensitivity and specificity (point nearest the top left hand corner of the graph) and these were calculated. Bland & Altman (1986) plots were obtained to analyse the differences for each subject between both of the indirect estimates of GFR with the gold standard measurement.

For cystatin C and creatinine/ height, concentrations were normalised against the mean value for the 'normal' group (actual concentration/ mean concentration) to enable direct comparisons of the raw data to be made. In addition, comparisons of change in calculated GFR for each variable from the models derived from the same data were made. The two year data were analysed using a general linear, UNIANOVA model, involving calculation of the best fit line of individual changes in each variable over time, compared to baseline values (section 3.6).

4.3 Results

4.3.1 Linear regression

When all patient data were included, there was better correlation between 1/cystatin C and EDTA GFR than with height/ creatinine (Figure 4.3.1). The linear regression model for estimated GFR derived from height/ creatinine could not be reapplied to the data however, due to curvature suggested by the standardised regression residuals, associated with inclusion of the 'normal' group. When only those with CRI were included in the analysis, there was equally good correlation between the indirect methods, and suitable models could be obtained for both methods.

4.3.2 Sensitivity and specificity

To examine the suitability of the indirect methods as screening tools for differentiating CRI from those with 'normal' renal function, children were classified based on a cut-off of $\leq$ 75 ml/min/1.73m^2 for CRI, and ROC curves were obtained (Zweig & Campbell, 1993). Cystatin C and creatinine/ height exhibited similar sensitivity, specificity and area under the curve (Table 4.3.2 and Figure 4.3.2.1). Both lacked sensitivity (67.2%) at 100% specificity. Optimum ROC points however, gave better overall sensitivity and specificity, with 90.6% and 84.8% respectively for cystatin C and 78.1% and 93.5% for creatinine/ height.

The results may vary depending on the cut-off used to categorise those with 'normal' renal function from those with CRI. A GFR of 75 ml/min/1.73m^2 was used for the purpose of this research, based on the classification used for the NAPRTCS data (Fivush et al, 1998). To further examine the sensitivity and specificity of cystatin C and creatinine/ height as markers for detecting early renal failure, the data were re-analysed using additional cut-offs of 80, 85 and 90 ml/min/1.73m^2. ROC analysis was repeated for the variable cut-offs, to compare sensitivity in classification between 'normal' renal function and CRI (Table 4.3.2). An improvement in the area under the curve and in sensitivity and specificity, particularly for creatinine/ height at 100% specificity were observed at cut-offs of 80-85 ml/min/1.73m^2 (Table 4.3.2 & Figure 4.3.2.2). Although creatinine/ height was more sensitive than cystatin C at 100% specificity for most cut-off values, cystatin C exhibited greater areas under the curve and better sensitivity and specificity overall at the optimum ROC point.

4.3.3 Reference ranges and cystatin C cut-off concentrations

If the data are normally distributed, the reference range is quoted as 2 SD either side of the mean. For skewed data, the values at the 2.5^{th} and 97.5^{th} percentiles are usually taken. Cystatin C data were deemed to be normally distributed within each group, whereas plasma creatinine exhibited little distinction in distribution between the extreme values and those represented by the main body of the data, and hence percentiles were used. The reference range quoted by Finney et al (2000) for cystatin C measurements in children with 'normal' kidney function was 0.5 – 1.27 mg/l. The study data were analysed in the same laboratory as that of Finney and produced a similar normal range (Table 4.3.3.1). There was significant overlap in reference ranges between the GFR groups however, particularly for plasma creatinine between those with normal renal function and mild CRI. Use of plasma creatinine/ height reduced the amount of overlap between groups but cystatin C gave the clearest segregation between reference ranges for the groups. Using ROC curve co-ordinates at a cut-off of 80 ml/min/1.73m^2, for 100% specificity, a cystatin C level of 1.26 mg/l gave 67% sensitivity and a creatinine/ height value of 0.56 μmol/ l/ cm gave 76% sensitivity, in detecting the difference between those with 'normal' renal function and CRI (Table 4.3.2).

Varying cut-off serum cystatin C and plasma creatinine/ height concentrations were chosen equivalent to those giving maximised sensitivity and specificity at varying EDTA GFR cut-offs to explore classification in more detail (Table 4.3.3.2). The percentage of children that were correctly classified as having 'normal' renal function, mild CRI or more severe CRI were observed. The cystatin C concentration for 100% specificity (1.26 mg/l) correctly classified 98% of children with 'normal' renal function, but only detected 23% of those with mild CRI, whereas a creatinine/ height of 0.56 μmol/ l/ cm correctly identified 42% of children as having mild CRI. All children with moderate and severe CRI had cystatin C and creatinine/ height concentrations above the cut-off value. Cystatin C concentrations of 1.035 mg/l and 0.995 mg/l, equivalent to the optimum ROC points however, significantly improved the classification of those into mild CRI or 'normal' renal function such that approximately 80% were correctly classified. There was a wider range of cut-off values for creatinine/ height for the optimum ROC points, as would be expected from the ROC curves (Figures 4.3.2.1 & 4.3.2.2). A value of 0.51 μmol/ l/ cm, equivalent to a cut-off EDTA GFR of 80-85

ml/min/1.73m^2 only correctly classified approximately 50% of children as having mild CRI rather than 'normal' renal function. This was improved to 75% being correctly classified into either group if the value of 0.48 μmol/ l/ cm, equivalent to a cut-off of 90 ml/min/1.73m^2 was taken.

4.3.4 Level of agreement of indirect methods with EDTA GFR

Bland and Altman plots (1986) were used to assess the level of agreement of the indirect methods with EDTA GFR. For all data, the calculation of GFR [GFR = (117/ cystatin C) – 29] derived from the linear regression model for cystatin C appeared to show much greater spread for those with 'normal' renal function (Figure 4.3.4.1). As a result, although the mean GFR as estimated by serum cystatin C was equivalent to the mean EDTA GFR, the standard deviation was large and to encompass 95% of the data, the variation was equivalent to the mean GFR ± 32. If the 'normal' group were excluded from the comparison, the repeated linear regression model [GFR = (81/ cystatin C) – 8] resulted in halving of the variation about the mean (Figure 4.3.4.2). A similar pattern emerged for creatinine/ height, but as the linear regression model for all data could not be calculated, the equation similar to that of Counahan et al (1976) used in our unit, where K = 40 was thus applied (Figure 4.3.4.3). The spread about the mean was slightly greater compared to cystatin C (GFR ± 36) for all data. Exclusion of the 'normal' group enabled linear regression to be conducted and the derived model was used to estimate GFR on those with CRI [GFR = (36 x height/ creatinine) – 4]. There was equally good agreement with EDTA GFR using creatinine/ height rather than cystatin C and the spread of data was significantly reduced when those with 'normal' renal failure were excluded (Figure 4.3.4.4).

4.3.5 Estimation of progression of CRI

Progression of CRI over the two year period could be assessed using either of the two indirect methods for estimation of GFR, as described by the derived equations for those with CRI. Unfortunately, they could not be compared to the gold standard as this was only obtained at baseline. Use of normalised values for cystatin C and creatinine/ height reflect the degree of change in GFR at 6 monthly intervals over the two year period, whilst excluding the introduction of errors involved in using a derived model to estimate GFR. The values used for normalisation were the mean serum cystatin C

concentration (0.9 mg/l) and creatinine/ height value (0.43 μmol/ l/ cm) for the 'normal' group (n=46). For the cohort as a whole, the mean change in normalised creatinine/ height and cystatin C over 1 and 2 years respectively were virtually identical (Table 4.3.5.1). The largest increase in either normalised creatinine/ height (1.07) or cystatin C (0.92) concentrations were seen in those with severe CRI. For creatinine/ height, a stepwise increase in the degree of change in normalised values was observed with increasing severity of CRI, whereas this was not observed for cystatin C, where those with moderate CRI exhibited a smaller increase in normalised cystatin C concentrations over time than those with mild CRI.

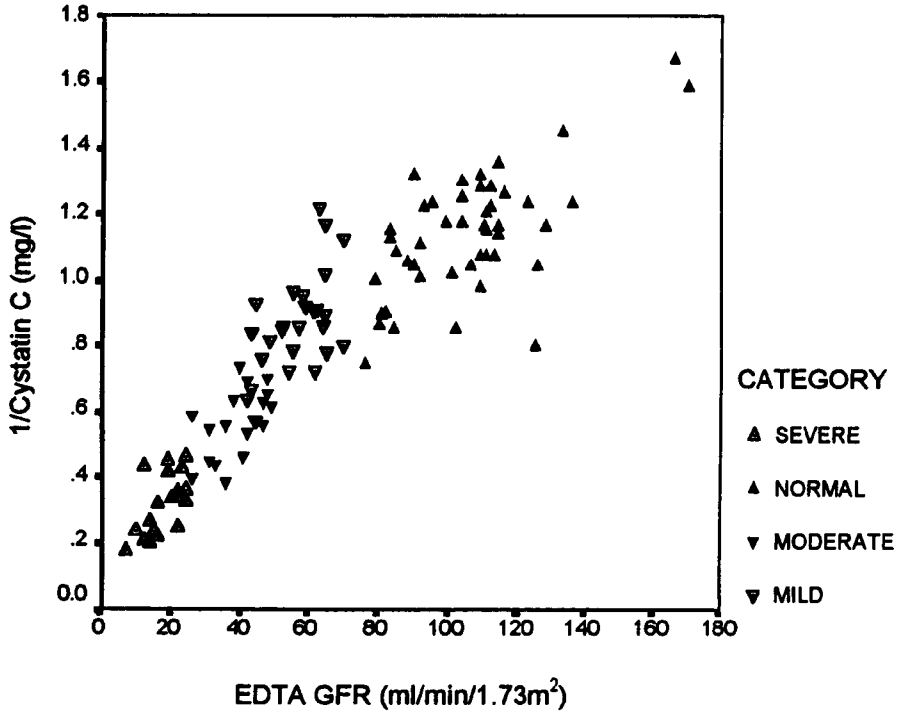
The general linear UNIANOVA model can be used to compare changes between groups or individuals over a period of time by calculating a 'best fit' line between the observations for a specified variable. Figures 4.3.5.1 & 4.3.5.2 (appendix 1) show the changes between groups and between individuals within the groups over the 2 year period. A significant reduction in GFR and significant differences between individuals over time were observed in all groups of CRI, when determined by normalised creatinine/ height (Table 4.3.5.1). When calculated using normalised cystatin C concentrations however, differences between individuals within each group were significant for those with severe CRI, but surprisingly not for those with mild and moderate CRI (not tabled). There also appeared to be no significant reduction in GFR for those with moderate CRI, according to normalised cystatin C concentrations.

Individual changes in renal function at 1 and 2 years, as estimated by plasma creatinine/ height and serum cystatin C, for mild, moderate and severe CRI are depicted in Tables 4.3.5.2 - 4.3.5.4 (appendix 1) respectively. A summary of these data, drawing comparisons between estimated GFR based on creatinine/ height and cystatin C are illustrated in Table 4.3.5.5. The greatest mean reduction in estimated GFR did not equate to the greatest change in normalised values. Using creatinine/ height, the estimated mean reduction in GFR over 2 years was greatest for those with mild CRI (-8.4 ml/min/1.73m^2), and of a similar order for those with moderate and severe CRI (-5.5 & -5.1 ml/min/1.73m^2 respectively). The mean reduction in estimated GFR from cystatin C was similar to that determined by creatinine/ height for those with mild and severe CRI, but half of that determined for those with moderate CRI. In children with mild CRI, there was little data for cystatin C derived GFR, but creatinine/ height

showed 7 children to exhibit substantial deterioration in their renal function over the two year period ($\geq$ -10 ml/min/1.73m^2) and conversely, 4 children exhibited a small improvement in renal function. The majority of those with moderate CRI showed a modest decline in renal function (0 to –9 ml/min/1.73m^2) and 3-4 children showed an improvement. For those with severe CRI, the majority who reached the end of the 2 year period continued to exhibit deterioration in renal function, and 6 children did not reach the end of the study due to the need for dialysis or pre-emptive transplantation. Eight children (44%) from those where estimation of GFR by creatinine/ height was available with mild CRI, were suggested to have moved to the moderate group, whereas there was little data available for estimation of GFR by cystatin C (Table 4.3.5.2; appendix 1). From what was available, 40% were considered to have moved groups. Six children (30%) with moderate CRI were considered to have moved to the severe group by creatinine/ height, compared with 2 children (17%) from available data by cystatin C (Table 4.3.5.3; appendix 1). One child appeared to demonstrate an improvement in GFR that moved him up to the mild group by creatinine/ height. For those with severe CRI, one child was suggested to have moved up to the moderate group by cystatin C, but not by creatinine/ height. Estimated changes by both methods for the remainder of the severe group seemed to be in general agreement with each other. Unfortunately these observations could not be compared with a gold standard.

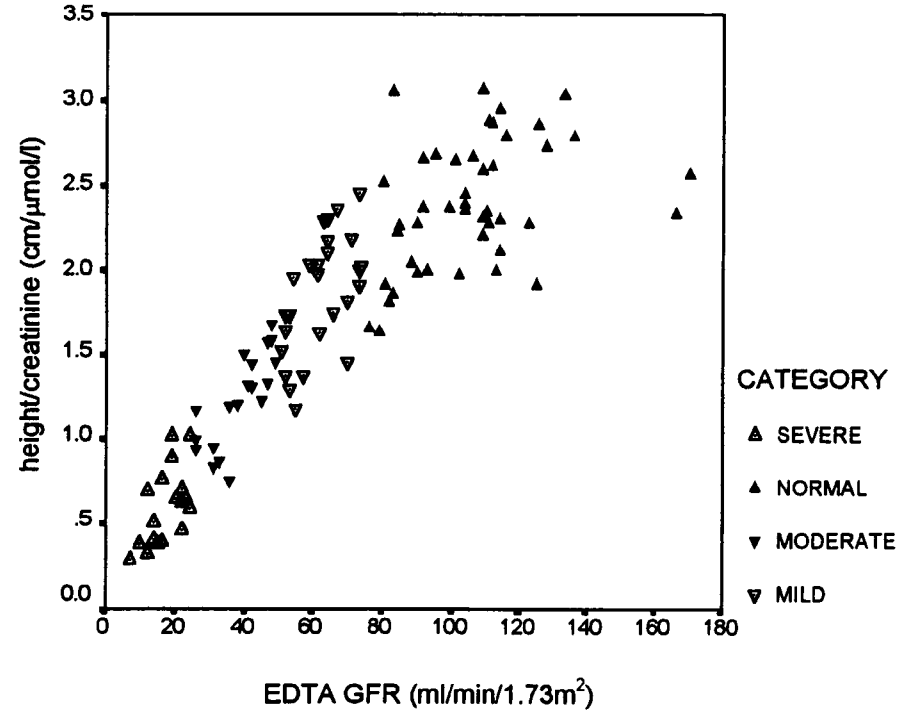
Figure 4.3.1 Linear regression with differentiation of groups

Cystatin C



All data – [R=0.919; F=589; 1,108df, p<0.0001]
CRI data – [R=0.924; F=363; 1,62df, p<0.0001]

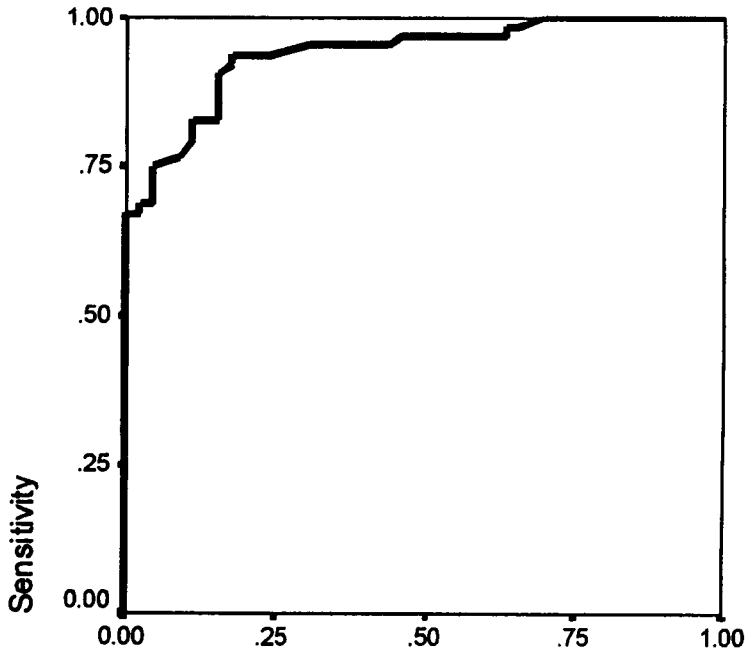
Height/creatinine



All data – [R=0.883; F=383; 1,108df, p<0.0001]
CRI data – [R=0.927; F=377; 1,62df, p<0.0001]

Figure 4.3.2.1 Receiver operating characteristic curves (cut-off 75 ml/min/1.73m^2)

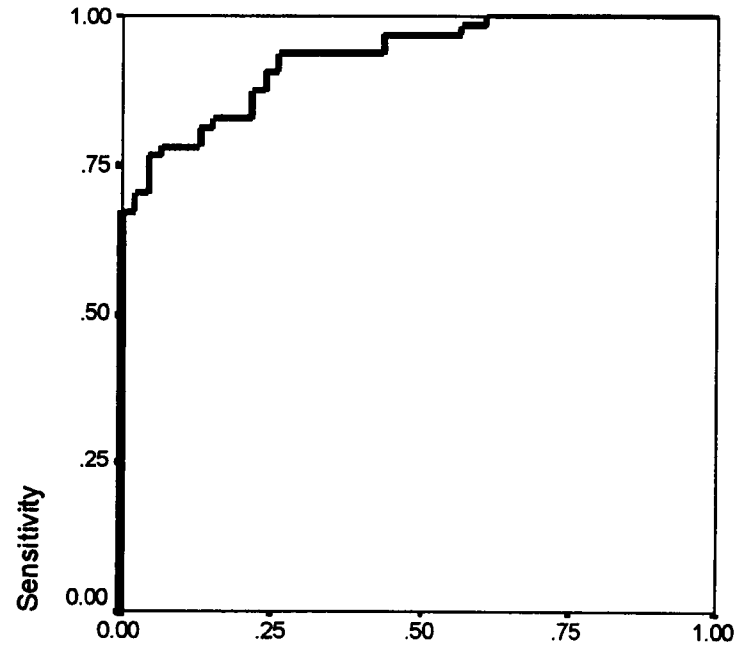
Cystatin C



Diagonal segments are produced by ties.

Area under the curve = 0.941

Creatinine/ height

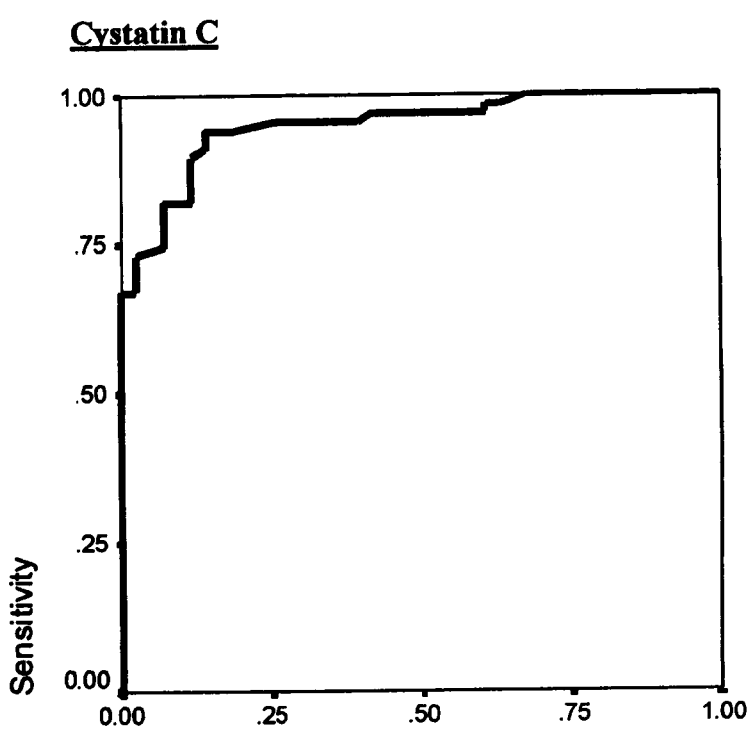


Area under the curve = 0.931

Table 4.3.2 Receiver operating characteristic co-ordinates between 'normal' and CRI (using variable cut-offs)

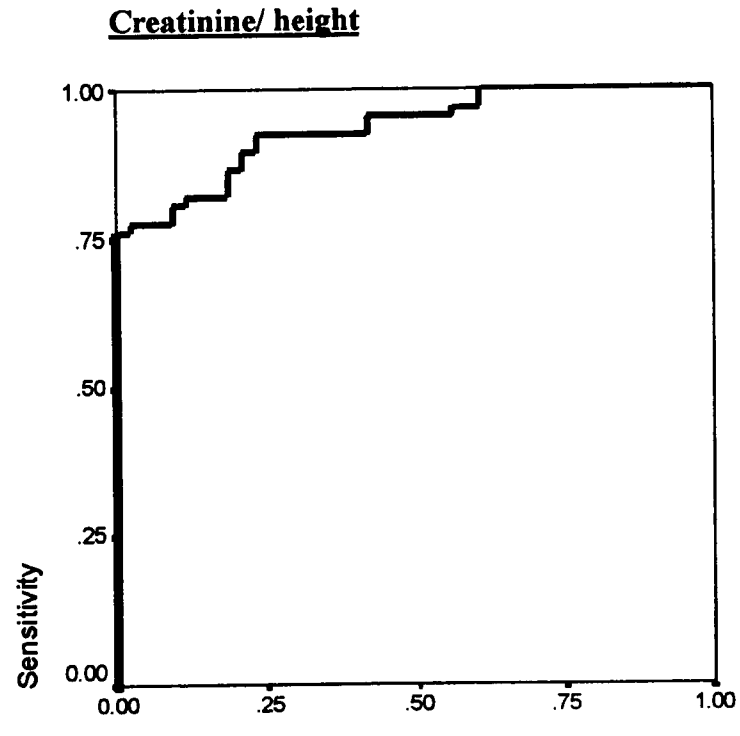
Cut-off (GFR ml/min/1.73m^2) for 'normal' from CRI	Cystatin C (mg/l)				Creatinine/ height (μmol/ l/cm)			
	75	80	85	90	75	80	85	90
N= ('normal' renal function)	46	43	37	34	46	43	37	34
Area under curve	0.941	0.95	0.948	0.934	0.931	0.935	0.932	0.936
Sensitivity (%) if specificity = 100%	67.2	67.2	61.6	59.2	67.2	76.1	75.3	72.4
Corresponding concentration	1.345	1.26	1.26	1.26	0.621	0.563	0.524	0.524
'Optimum ROC point' Sensitivity (%)	90.6	89.6	91.9	91.2	78.1	80.6	79.5	85.5
'Optimum ROC point' Specificity (%)	84.8	88.4	90.4	86.8	93.5	90.7	94.6	88.2
Corresponding concentration	1.035	1.035	0.995	0.995	0.546	0.508	0.504	0.475

Figure 4.3.2.2 Receiver operating characteristic curves (cut-off 80 ml/min/1.73m^2)



Diagonal segments are produced by ties.

Area under the curve = 0.950



Area under the curve = 0.935

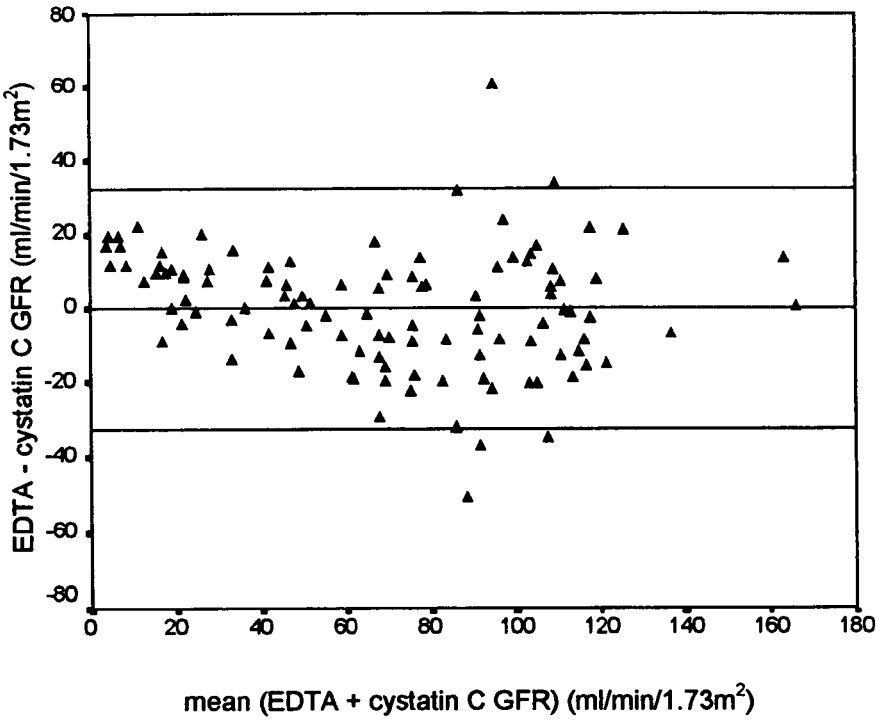
Table 4.3.3.1 Reference ranges determined from data by both the parametric and non-parametric methods

	Group (n=)	Parametric	Non-parametric
Serum cystatin C	'Normal' (46)	0.6 – 1.2	0.61 – 1.32
(mg/ l)	Mild (26)	0.72 – 1.72	0.81 – 1.85
	Moderate (19)	0.91 – 3.03	1.21 – 3.29
	Severe (19)	1.33 – 5.57	1.57 – 5.79
Plasma creatinine	'Normal' (46)	26 – 84	34 – 110
(μmol/ l)	Mild (26)	36 – 120	46 – 120
	Moderate (19)	40 – 218	60 – 241
	Severe (19)	49 – 427	126 - 465
Plasma creatinine/	'Normal' (46)	0.29 – 0.57	0.33 – 0.61
height (μmol/ l/ cm)	Mild (26)	0.32 – 0.8	0.41 – 0.84
	Moderate (19)	0.44 – 1.28	0.59 – 1.32
	Severe (19)	0.47 – 3.35	0.98 – 3.44

Table 4.3.3.2 Percentage correctly classified as having CRI or 'normal' renal function based on variable cut-off plasma/ serum concentrations, obtained from Table 4.3.2.

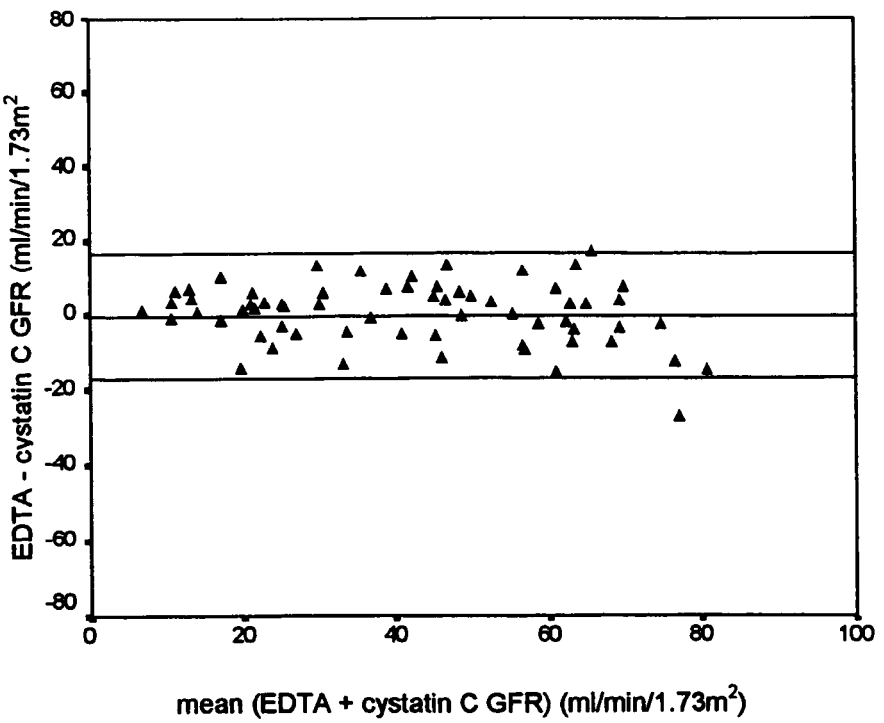
Group (N=)	N= (%) correctly classified **Cystatin C (mg/l)**			N= (%) correctly classified **Creatinine/ height (μmol/ l/ cm)**		
	1.26	1.035	0.995	0.56	0.51	0.48
Normal (46)	45 (98)	39 (85)	37 (80)	44 (96)	40 (87)	35 (76)
Mild (26)	6 (23)	20 (77)	22 (85)	11 (42)	13 (50)	19 (73)
Moderate (19)	19 (100)	19 (100)	19 (100)	19 (100)	19 (100)	19 (100)
Severe (19)	19 (100)	19 (100)	19 (100)	19 (100)	19 (100)	19 (100)

Figure 4.3.4.1 Bland & Altman plot for cystatin C calculation of GFR from model for all data



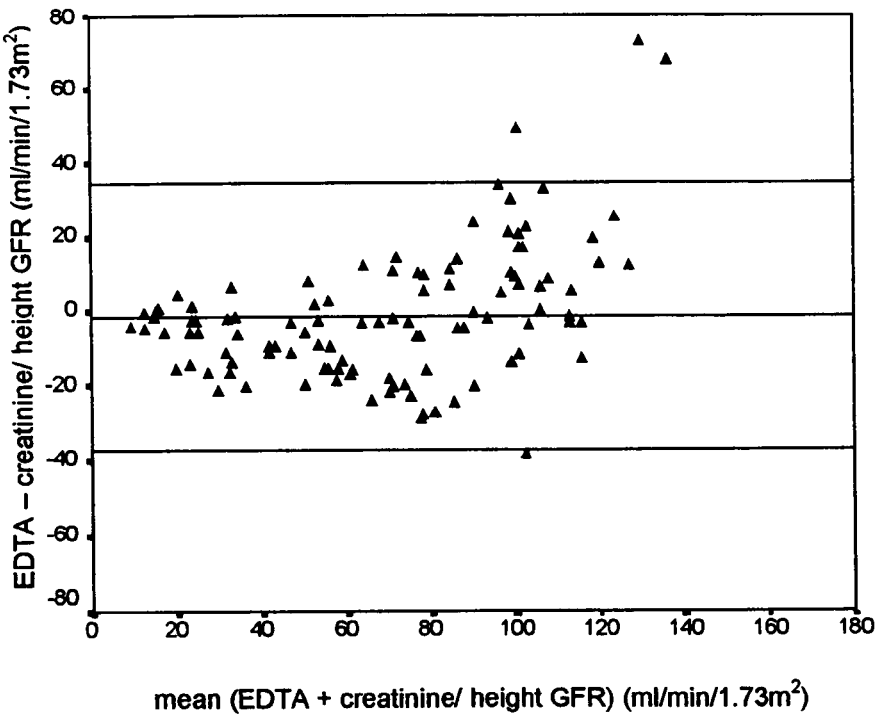
Mean –0.16
± SD 16.09

Figure 4.3.4.2 Bland & Altman plot for cystatin C calculation of GFR from model (adjusted for CRI data only)



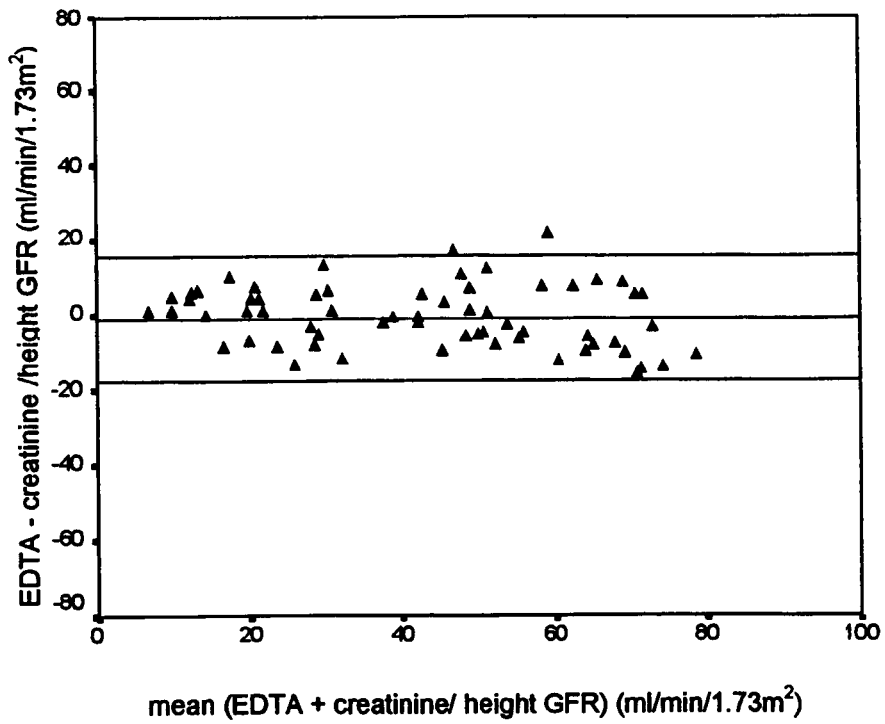
Mean -0.29
± SD 8.31

Figure 4.3.4.3 Bland & Altman plot for standard creatinine/ height calculation (k=40) of GFR for all data



Mean –1.41
± SD 18

Figure 4.3.4.4 Bland & Altman plot for model calculation of creatinine/ height (adjusted for CRI data only)



Mean -0.88
± SD 8.18

Table 4.3.5.1 Change (Δ) in renal function over the 2 year period between groups as determined by normalised values

CRI group	Δ in normalised creatinine/ height (μmol/l/cm) N= number patients/ observations [mean (SD)]	Δ in normalised cystatin C (mg/l) N= number patients/ observations [mean (SD)]
All children		
End 1 yr	N= 54 [0.16 (0.33)]	N= 41 [0.16 (0.40)]
End 2yrs	N= 50 [0.49 (0.64)]	N= 27 [0.48 (0.55)]
Significance	N=275 [F=117; 1df, p<0.001]	N=202 [F=16; 1df, p<0.001]
Mild CRI		
End 1 yr	N= 20 [0.11 (0.17)]	N= 16 [0.09 (0.21)]
End 2yrs	N= 18 [0.17 (0.21)]	N= 5 [0.22 (0.09)]
Significance	N=101 [F=28; 1df, p<0.001]	N=67 [F=12; 1df, p=0.002]
Moderate CRI		
End 1 yr	N= 20 [0.22 (0.34)]	N= 16 [0.20 (0.48)]
End 2yrs	N= 19 [0.39 (0.38)]	N= 11 [0.14 (0.26)]
Significance	N=99 [F=37; 1df, p<0.001]	N=72 [F=0; 1df, p=0.524]
Severe CRI		
End 1 yr	N= 14 [0.15 (0.46)]	N= 9 [0.15 (0.46)]
End 2yrs	N= 13 [1.07 (0.93)]	N= 11 [0.92 (0.58)]
Significance	N=75 [F=44; 1df, p<0.001]	N=63 [F=30; 1df, p<0.001]

Significance is determined by UNIANOVA for changes over time, observations made at 6 monthly intervals for 2 yrs

Table 4.3.5.5 Summary of change in renal function over 2 years between groups as determined by estimated GFR from plasma creatinine/ height or serum cystatin C concentrations

	Mild CRI		Moderate CRI		Severe CRI	
	Creatinine/ height	Cystatin C	Creatinine/ height	Cystatin C	Creatinine/ height	Cystatin C
Change in estimated GFR * Mean (SD) {n=}	-8.4 (9.5) {18}	-9.4 (2.1) {5}	-5.5 (4.9) {19}	-2.4 (5.8) {11}	-5.1 (4.6) {13}	-5.9 (4.0) {11}
No. with GFR change ≥ -20 ml/min/1.73m²	4	0	1 child reached ESRD		6 children reached ESRD	
No. with GFR change -10 to -19 ml/min/1.73m²	3	2	3	1	1	0
No. with GFR change -9 to 0 ml/min/1.73m²	7	3	13	6	10	10
No. with an improvement in GFR (> 0 ml/min/1.73m²)	4	0	3	4	2	1

Creatinine/ height (μmol/l/cm); cystatin C (mg/l); ESRD, End Stage Renal Disease

* GFR (ml/min/1.73m²) models: (36 x height (cm)/ creatinine (μmol/l)) – 4; (81/ cystatin C) – 8.

4.4 Discussion

Identification of patients with mildly impaired GFR in the so-called 'creatinine blind area' (i.e. where plasma creatinine has yet to rise, despite impaired kidney function), or to detect subtle changes in deteriorating renal function is not yet possible with confidence, without undertaking an invasive clearance test. The challenge therefore exists to find a more sensitive, non-invasive, simple marker of GFR, such as the proposed measurement of serum cystatin C.

To test the hypothesis that cystatin C is a suitable marker for detecting mild CRI, this study was set out to compare this variable with the currently used modified estimate of GFR from patient height and plasma creatinine (Counahan et al, 1976). It is accepted that plasma creatinine alone does not correlate well with actual GFR in children, due to its dependence on age and body size and hence was not used in this comparison. Simple linear regression with inclusion of the 'normal' group did not accurately describe the relationship between creatinine/ height and EDTA GFR due to apparent curvature in the standardised regression residuals associated with higher EDTA GFR values (i.e. those with 'normal' renal function). The inability to use linear regression has not been acknowledged previously. Coll et al (2000) carried out linear regression on only those with a GFR $\leq$ 75 ml/min/1.73m^2 for correlation, despite having data on a control group with 'normal' kidney function. When their control group for plasma creatinine were included graphically, a similar pattern to that noted in this present study seemed to exist. To enable determination of the marker most sensitive for identifying mild CRI, Coll and colleagues (2000) re-calculated a line by linear regression that better fitted the distribution of values of patients and controls. A graph could then be developed from which projections could be made to detect the marker that first started to increase over the normal range of GFR. In contrast, it was not felt appropriate to use linear regression similarly in this study, due to apparent curvature of data if those with a GFR above 75 ml/min/1.73m^2 were included in the analysis. Coll et al (2000) suggested that a mild reduction in GFR was detected more easily by serum cystatin C than creatinine concentration because cystatin C levels started to increase to greater than normal values when their gold standard GFR was approximately 88 ml/min/1.73m^2 compared to 75 ml/min/1.73m^2 for creatinine.

If those with 'normal' renal function were excluded from the linear regression, suitable models for estimating GFR could be applied to the data for both cystatin C and creatinine/ height. The derived equations could subsequently be reapplied to the data to estimate the change in GFR over a 2 year period. Exclusion of those with 'normal' renal function produced equally good correlation between height/ creatinine and 1/ cystatin C with EDTA GFR (R=0.927 vs 0.924), but as acknowledged by Skinner et al (1994), the use of correlation coefficients is misleading, often meaningless and the significance value is irrelevant. A highly significant correlation coefficient may exist despite considerable scatter. The correlation coefficient measures linear association rather than agreement and it would be surprising if the results obtained from two methods designed to measure the same quantity were not related. Therefore Bland & Altman (1986) plots were also conducted to observe the level of agreement between the two methods with EDTA GFR.

Bland & Altman analysis gave a negligible bias for both cystatin C and creatinine/ height as described by others (Bokenkamp et al, 1998b), whether data included the 'normal' group or not. The spread about the mean however increased with rising GFR for both indirect methods, as also noted by Bokenkamp et al (1998b) and previously reported by Skinner et al (1994), reflecting lower assay precision at low analyte concentrations. The scatter (2SD) was slightly greater in the creatinine/ height than cystatin C based estimation of GFR (36 vs 32). Nevertheless, the study data represent an improvement in the limits of agreement of approximately 5-10 ml/min/1.73m^2 compared to previous reports (Bokenkamp et al, 1998b; Kilpatrick et al, 2000). Exclusion of those with 'normal' renal function significantly reduced the spread about the mean in both cases, and both were equally accurate in estimating GFR for children with CRI, to a 2 SD spread about the mean EDTA GFR of 16 ml/min/1.73m^2. The increasing spread does not appear to occur until the GFR exceeds approximately 100 ml/min/1.73m^2 and hence should not negate use of either of the indirect methods for suggesting whether a child has mild CRI or not. Neither method is accurate enough to replace an EDTA GFR where an exact measurement is required however, but it should also be acknowledged that considerable intra-individual variability exists in using the gold standard measurement. Some of the scatter noted in the Bland & Altman analysis may not reflect poor performance of the endogenous markers tested but may be attributable to fluctuations in the gold standard, associated with error in the counting of

radioactivity, the measurement and injection of the radioactive substance, weighing of materials and timing of sampling.

Using ROC analysis, both measures were shown to lack diagnostic efficacy at 100% specificity in identifying patients with impaired renal function, unlike that described by Coll et al (2000), who reported very good sensitivities in adults at this highest level of specificity (93.4% for cystatin C and 86.8% for creatinine). Diagnostic accuracy of the indirect methods in this study was greatly improved if a specificity of between 85-95% was deemed acceptable, as reported by Bokenkamp et al (1998b). Cystatin C data showed marginally better sensitivity and specificity at the optimum ROC point, apart from sensitivities at 100% specificity, where at a cut-off of 80 ml/min/1.73m^2, cystatin C gave 67.2% sensitivity and creatinine/ height 76.1% sensitivity. The results of this study are similar to those reported by Stickle and colleagues (1998) who found cystatin C to be numerically superior, but not statistically different to creatinine at the optimum ROC point. Filler et al (1999) suggested that there was a non-significant tendency for the Schwartz formula to give better overall sensitivity, specificity and area under the curve than cystatin C for a cut-off of 90 ml/min/1.73m^2. These findings suggest that cystatin C is broadly equivalent to creatinine/ height as a marker of GFR.

ROC analysis was repeated to observe sensitivity and specificity at varying GFR cut-offs, and a cut-off of 80-85 ml/min/1.73m^2 gave the greatest sensitivity, specificity and area under the curve values for both methods. The cut-off concentration at EDTA GFR's of 80-90 ml/min/1.73m^2 with 100% specificity for cystatin C, was equal to 1.26 mg/l. This value, which is very similar to that obtained by Newman et al (1995) in adults (1.25 mg/ l for a GFR < 72ml/min/1.73m^2), corresponds well to the upper limit of the normal reference range quoted for children by Finney et al (2000) of 1.27 mg/l, and the reference range from our data of 1.2 mg/l. These reference intervals are slightly lower than previously quoted reference intervals, possibly due to the difference in methods, associated with different standardisation procedures (Erlandsen et al, 1999). Aiming for 100% specificity (i.e. equivalent to the upper limit of the normal range for serum cystatin C) however, whilst ensuring that those with 'normal' renal function are not misclassified, will result in a large proportion of children with mild CRI remaining undetected. At the optimum ROC points, the equivalent cut-off cystatin C concentrations were between 0.995 - 1.035 mg/l, which significantly improved the

proportion of children correctly classified into having either normal renal function or mild CRI, with approximately 80% accuracy. An averaged cystatin C concentration of 1 mg/l could be used as a practical marker for determining whether the child exhibits a mild degree of CRI or not, and who would therefore benefit from closer medical and nutritional monitoring. Appropriate classification was less clear for creatinine/ height, as a cut-off of 90ml/min/1.73m^2, equivalent to a value of 0.48 μmol/ l/ cm, was required to correctly classify 75% of children as either having mild CRI or 'normal' renal function. Cut-offs less than this reduced the proportion of children correctly classified quite substantially. This supports the work of Coll and colleagues (2000) in suggesting that cystatin C is more accurate than creatinine for classification purposes. The best GFR cut-off for classification of children as having mild CRI or 'normal' renal function has not yet been elucidated, with varying figures between 75 – 90 ml/min/1.73m^2 being quoted as the lower limit for 'normal' kidney function. An attempt to establish an agreed classification for future clinical practice would be recommended.

It is not altogether surprising that cystatin C appears to be better than creatinine, as although it is acknowledged that creatinine is affected by body size, it is often not taken into consideration (Helin et al 1998; Ylinen et al, 1999; Coll et al, 2000). Swaminathan (2001) points out that muscle mass contributes little to the variation in plasma creatinine concentration in adults however, unless in extreme cases such as emaciation or body-building. Many adult renal patients nevertheless are emaciated, due to less aggressive nutritional support than that commonly provided for in children to promote growth. This may explain the discrepancy in published findings and why no significant differences were observed between the two indirect methods as described by this study and Filler et al (1999), when the effect of size in children was accounted for by correcting creatinine for height, using various height/ creatinine formulae.

Currently there does not appear to be any literature available in assessing whether cystatin C is more useful than creatinine/ height in monitoring progression of children with CRI and as Deinum & Derkx (2000) highlight, these questions need to be answered. Unfortunately, this study was not designed to address this, as repeat EDTA GFR's were not available at the end of the two year study to compare against our estimated GFR measurements, due to ethical reasons related to avoidance of undue exposure to radiation. The study does however, provide longitudinal observational data

for comparison of changes in estimated GFR from both variables. An increasing trend in apparent deterioration in renal function was observed with increasing severity, based on changes in normalised values for creatinine/ height. This might be expected, particularly in light of the increasing presence of proteinuria across the groups, which is recognised as a predictive marker of deterioration of renal function (Klahr et al, 1994; Wingen et al, 1997). This did not appear to be the case however, if change in estimated GFR over the two year period was assessed, using equations derived from the linear regression models for both variables. Creatinine/ height estimations showed the mean change in estimated GFR to be greatest for those with mild CRI, and similar in those with moderate and severe CRI. The reference ranges for both creatinine/ height and cystatin C broaden with increasing renal failure and hence the changes in absolute concentrations and therefore normalised values are likely to be greater accordingly. Conversely, a greater increase in absolute concentration will be necessary to produce an equivalent change in GFR with increasing severity of CRI, due to a percentage change effect. The net effect is likely to be an increase in normalised values accompanied by a smaller change in GFR with increasing severity of CRI. Nevertheless, the fact that approximately 44% children with mild CRI progressed into the moderate group over the 2 year period, as determined from estimated GFR's, compared with 30% for moderate to severe CRI and severe CRI to ESRD, supports the suggestion that those with mild CRI may have demonstrated a higher degree of progression than those with more severe CRI.

Mean reductions in GFR as estimated from plasma creatinine/ height over the two year period, were 8.4 ml/min/1.73m^2 in children with mild CRI and approximately 5 ml/min/1.73m^2 in the other two groups. A reduction of 5 ml/min/1.73m^2 over two years was also reported by Wingen et al (1997) for children with congenital abnormalities, which was the underlying diagnosis in approximately 80% of patients in this study, and no children exhibited glomerulonephropathies which are reported to be associated with a more rapid decline in renal function. Mean changes in normalised creatinine/ height and cystatin C at the end of 1 and 2 years respectively were of a similar order for the group as a whole, and for those with mild and severe CRI. There was a significant discrepancy between the methods for those with moderate CRI however, with no significant deterioration in GFR over the 2 year period being demonstrated by cystatin C. Only 17% of children with moderate CRI were considered to have progressed to

severe CRI by cystatin C, compared with the 30% suggested by GFR estimated from creatinine/ height.

The differences shown by cystatin C data are difficult to explain, due to the lack of research in this area. For those with moderate CRI, whether change in normalised values, UNIANOVA or estimated change in GFR are used, cystatin C did not pick up any significant changes in GFR over the 2 year period. It may be that the concerns raised by Keevil and colleagues (1998) of there being greater intra-individual variability in the measurement of cystatin C compared to creatinine are upheld by our mixed findings. This may be supported by the lack of variation noted between individuals within groups, in the change in normalised cystatin C concentrations over time. Although there is no gold standard to compare these results to, the lack of change in those with moderate CRI as determined by cystatin C is of concern and raises the question as to whether cystatin C may not be as reliable as creatinine/ height for tracking the progression of CRI in individuals over time.

Cystatin C has the potential to be a promising alternative to creatinine as an endogenous marker of GFR in children, as unlike plasma creatinine, serum cystatin C concentration is independent of the patient's age, weight, height, gender, body composition, is not secreted by renal tubules and is not affected by the presence of bilirubin, haemolysis or triglycerides in serum. It is suggested that from this study, although serum cystatin C may be marginally more sensitive than plasma creatinine/ height in classifying children correctly as to whether or not they had a degree of renal failure according to EDTA GFR, this difference would not warrant a change in present practice. At present, serum cystatin C measurement is more expensive than plasma creatinine. There is also concern that cystatin C may not be as reliable as creatinine in monitoring patients' renal function over time, but this needs validation using a gold standard for comparison. Neither method can be considered an exact measurement of GFR and should not therefore replace exogenous clearance examinations for exact quantification of GFR where required.

Chapter Five

BASELINE RESULTS

Baseline results involved observing differences in anthropometric indices, nutritional intakes and biochemical parameters at recruitment between the 4 groups of children (n = 125); those with 'normal' kidney function, mild, moderate and severe CRI (demographic data, tables 3.3.1-3.3.7). In this work, all available data obtained on all children entering into the study are included. Due to editorial decision, the published paper by Norman and colleagues (2000) only described baseline comparisons between the four groups of children who had completed a food diary at recruitment (n=95). The published results however, although a subset of the overall findings, do not differ significantly from the results detailed in this chapter.

5.1 Anthropometric evaluation and blood pressure

Individual height, weight, BMI and MUAC standard deviation scores and actual systolic and diastolic BP measurements at baseline are depicted in Tables 5.1.1-5.1.4 (appendix 2). No child with 'normal' renal function had a height SDS below –2 SDS, whereas one child with mild, 2 with moderate and 4 children with severe CRI had height scores lower than –2. BMI values were below –2 SDS for 2 children within each of the 4 groups, whereas BMI was above 2 SDS in 3 children with both 'normal' and mild CRI group and in 1 child with moderate CRI. No child with severe CRI was considered to be overweight (BMI > 2 SDS). MUAC SDS produced similar findings to BMI SDS. Comparisons between groups with 'normal' were non-significant for actual anthropometric measurements (Table 5.1.5). Statistical comparisons between the groups for weight, height, BMI and MUAC standard deviation scores are described in Table 5.1.6 and illustrated in Figure 5.1.1. Height was significantly lower compared to 'normal' in all children with CRI, with a stepwise reduction related to worsening severity of renal failure. Weight was significantly less in children with moderate and severe CRI. MUAC and BMI were significantly lower in those with severe CRI, with MUAC exhibiting the greater difference. A highly significant correlation between

MUAC and BMI was observed (Figure 5.1.2). Children with 'normal' kidney function appeared to have height and weight SDS scores above that for the normal population using the Child Growth Foundation data of 1990 (Freeman et al, 1995).

Systolic blood pressure SDS tended to be higher with worsening renal failure, becoming significant in children with moderate and severe CRI compared to 'normal' (Figure 5.1.3). Diastolic blood pressure SDS was significantly higher in all children with CRI compared to those with normal kidney function. The difference was greatest in those with severe CRI. Twenty eight percent of the 114 children with a height above 100cm if a boy (95cm if a girl) had a SBP of greater than or equal to 2 SDS (95^{th} percentile), of which 25% had 'normal' renal function, 19% had mild, 28% moderate and 53% severe CRI (Tables 5.1.1-5.1.4, appendix 2). For DBP, 18% of all children had a DBP greater than or equal to 2 SDS, of which 9% had 'normal' renal function, 15% had mild CRI, 17% moderate and 47% severe renal failure. Only 2 children in the mild group (7%) and 3 children (14%) with moderate CRI were in receipt of antihypertensives, whereas 9 children (47%) with severe renal failure were prescribed antihypertensives. (Tables 3.3.5-3.3.7).

Table 5.1.5 Comparison of mean anthropometric indices in relation to severity of CRI

Growth Parameter	Statistic	'Normal' (n=58)	Mild CRI (n=27)	Moderate CRI (n=21)	Severe CRI (n=19)
Weight (kg)	**Mean (SD)**	28 (14)	31 (18)	30 (18)	30 (13)
	95% CI of the mean	25 to 32	24 to 39	22 to 38	24 to 36
Height (m)	**Mean (SD)**	1.25 (0.22)	1.28 (0.24)	1.26 (0.28)	1.29 (0.24)
	95% CI of the mean	1.20 to 1.31	1.18 to 1.37	1.13 to 1.38	1.18 to 1.41
BMI (wt/ ht^2)	**Mean (SD)**	17.1 (2.8)	17.8 (4.1)	16.9 (2.5)	16.9 (2.5)
	95% CI of the mean	16.3 to 17.8	16.2 to 19.4	15.7 to 18.8	15.7 to 18.1
MUAC (cm)	**Mean (SD)**	20.4 (3.9)	21.4 (5.2)	20.7 (5.5)	20.1 (3.6)
	95% CI of the mean	19.4 to 21.4)	19.3 to 23.4	18.2 to 23.2	18.3 to 21.9

wt, weight; ht, height; BMI, body mass index; MUAC, mid upper arm circumference

Table 5.1.6 Comparison of mean weight, height, BMI and MUAC SDS in relation to severity of CRI

Growth Parameter	Statistic	'Normal' (n=58)	Mild CRI (n=27)	Moderate CRI (n=21)	Severe CRI (n=19)
Weight SDS	**Mean (SD)**	0.28 (1.01)	-0.08 (1.22)	-0.47 (1.47)	-1.32 (1.04)
	95% CI of the mean	0.01 to 0.55	-0.56 to 0.4	-1.13 to 0.20	-1.8 to -0.82
	95% CI difference		-0.17 to 0.89	0.16 to 1.32	1.00 to 2.20
	p=			0.012	<0.001
Height SDS	**Mean (SD)**	0.19 (1.02)	-0.31 (1.00)	-0.58 (1.21)	-1.55 (1.10)
	95% CI of the mean	-0.07 to 0.46	-0.71 to 0.08	-1.13 to -0.04	-2.08 to -1.02
	95% CI difference		0.01 to 1.00	0.24 to 1.31	1.18 to 2.30
	p=		0.044	0.005	<0.001
BMI SDS	**Mean (SD)**	0.21 (1.10)	0.10 (1.30)	-0.10 (1.39)	-0.44 (1.07)
	95% CI of the mean	-0.08 to 0.50	-0.42 to 0.61	-0.73 to 0.53	-0.96 to 0.07
	95% CI difference		-0.44 to 0.66	-0.29 to 0.91	0.03 to 1.27
	p=				0.041
MUAC SDS	**Mean (SD)**	0.39 (1.00)	0.27 (0.97)	-0.05 (1.14)	-0.58 (0.93)
	95% CI of the mean	0.12 to 0.65	-0.12 to 0.65	-0.57 to 0.47	-1.05 to -0.12
	95% CI difference		-0.34 to 0.59	-0.07 to 0.95	0.43 to 1.51
	p=				0.001

SDS, standard deviation score
p values from one-way ANOVA with LSD post hoc test is given for comparison of groups with 'normal'

Figure 5.1.1 Comparison of mean weight, height, BMI & MUAC SDS in relation to severity of CRI

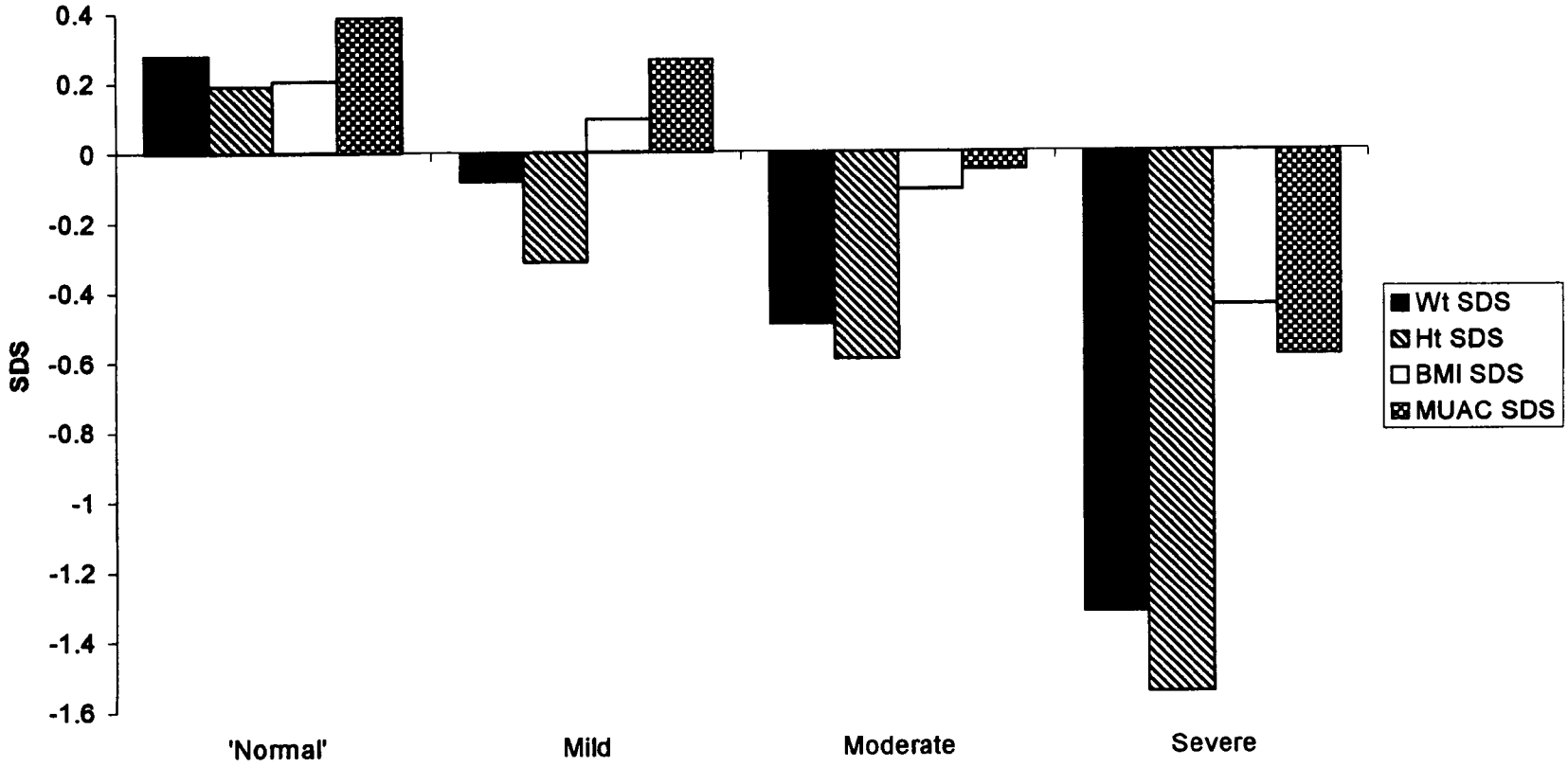
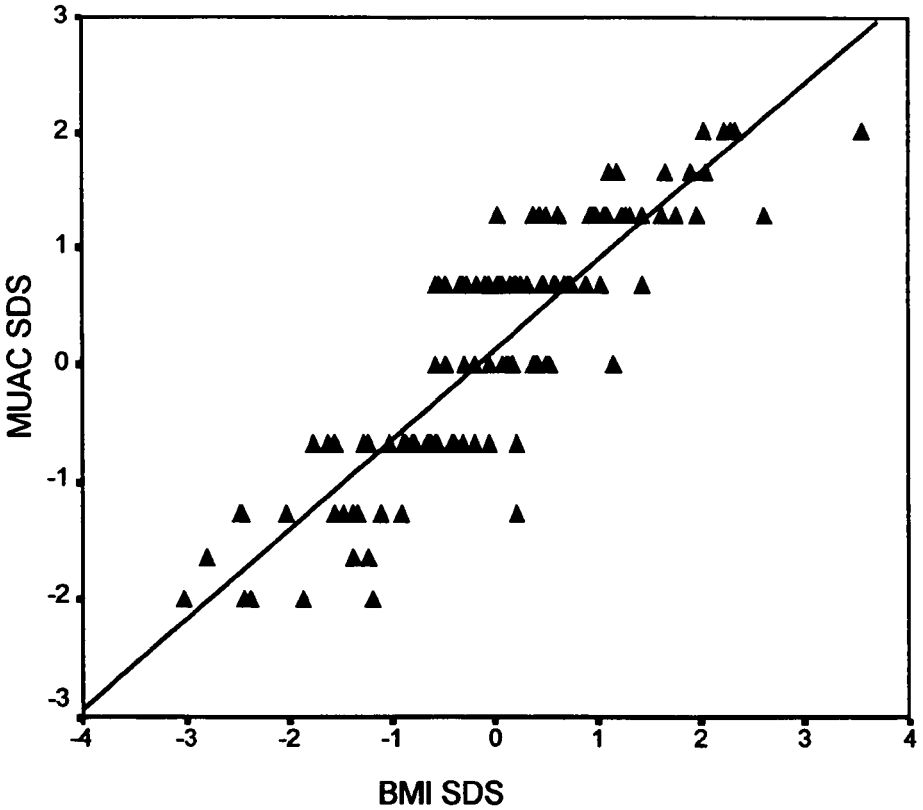


Figure 5.1.2 Correlation between MUAC & BMI SDS

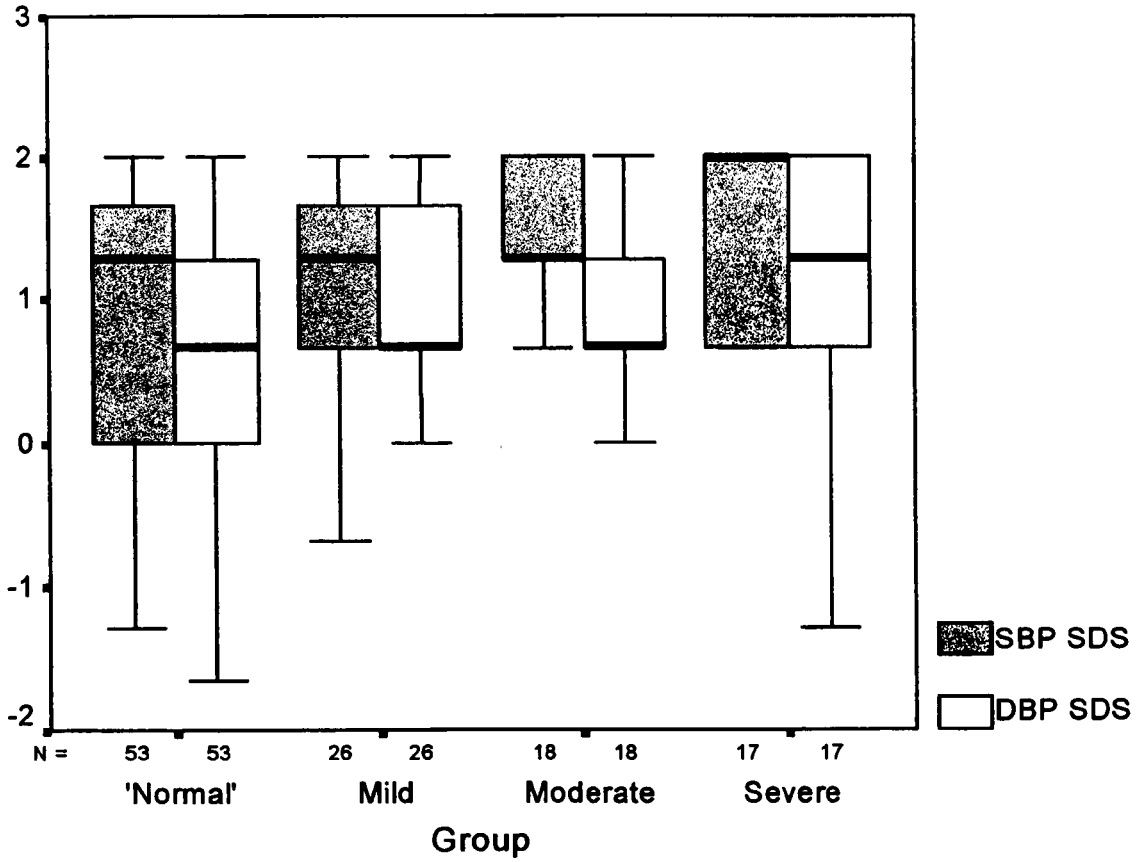


MUAC, mid upper arm circumference; BMI, body mass index;
SDS, standard deviation score;

$y = 0.129 + 0.768x$ [R^2=0.765; F=397; 1,122df, $p<0.001$]

Note: Due to unavailability of a computerised package for converting MUAC measurements into continuous data for centiles and SDS, the equivalent SDS for tabled discreet centiles were used, resulting in discreet SDS data

Figure 5.1.3 Comparison of systolic and diastolic blood pressure SDS with severity of CRI



	'Normal'	Mild	Moderate	Severe
SBP SDS				
Mean (SD)	0.82 (1.05)	1.07 (0.81)	1.32 (0.61)	1.49 (0.63)
95% CI mean	0.53 - 1.11	0.75 - 1.40	1.02 - 1.63	1.16 - 1.82
95% CI diff.		-0.67 - 0.16	-0.99 - -0.03	-1.16 - -0.18
P=			0.038	0.008
DBP SDS				
Mean (SD)	0.46 (0.99)	0.95 (0.68)	0.97 (0.62)	1.13 (1.01)
95% CI mean	0.18 - 0.73	0.68 - 1.23	0.66 - 1.28	0.61 - 1.65
95% CI diff.		-0.92 - -0.08	-0.99 - -0.04	-1.17 - -0.19
P=		0.02	0.034	0.007

SBP, systolic blood pressure; DBP, diastolic blood pressure
SDS, standard deviation scores (discreet data)
95% CI diff., 95% confidence interval of the difference
P values from oneway ANOVA with LSD post hoc test for comparison with 'normal'

5.2 Nutrient intake

Energy and protein

Individual energy and protein intakes for those children within each group who completed food diaries at baseline are listed in tables 5.2.1-5.2.4 (appendix 2). Prior to nutrient supplementation, 9% of children with both 'normal' renal function and mild CRI were suggested to have energy intakes ≤ 80% EAR, whereas 16% of those with moderate and 44% of children with severe CRI were considered to have low energy intakes. Median and interquartile ranges for energy intake when expressed as a percentage of the EAR, with and without inclusion of the energy provided by nutritional supplements, is illustrated in Figure 5.2.1. Table 5.2.5 depicts the median and interquartile range for energy when expressed as a total per kg actual body weight, with and without inclusion of the energy derived from nutritional supplements. Compared to 'normal', children with severe CRI had a significantly lower median intake of energy when expressed as a % of EAR or kcal/kg actual body weight, when the nutrition provided by nutritional supplements was not included in the analysis. Provision of nutritional supplements brought the suboptimal energy intakes in those with severe CRI back to intakes more in keeping with the other groups. One child with mild CRI received an energy supplement providing 6.8% of the total energy intake, two children in the moderate group received supplements contributing 32% and 35% to total energy intake, and seven children with severe renal failure were in receipt of one or more nutritional products, providing between 9–74% of their total energy intake.

Table 5.2.5 also illustrates the median and interquartile range for protein intakes when expressed as a percentage of total energy intake, with and without inclusion of the energy derived from nutritional supplements. Protein intake was also expressed as a factor of body weight, but this was not influenced by nutritional supplements, as in only one child did the supplement contain protein. Children with severe CRI had a significantly lower median intake of protein when expressed as a % of energy intake compared to 'normal', when the nutrition provided by nutritional supplements was included in the analysis. This was not significant however, when nutritional supplements were not accounted for, or when protein was expressed per kg actual body weight.

Fats and carbohydrate

Total fat intake and the contribution made from the various types of fatty acids, total carbohydrate and sugar intakes were all expressed as a percentage of total supplemented energy intake and tabled for each individual within each group (Tables 5.2.6 - 5.2.9, appendix 2). The proportion of children whose fatty acid intake reflected that recommended, improved with worsening renal failure, increasing from 9% of children with mild CRI with a saturated fat intake < 11% total energy intake and 13% with a polyunsaturated fat intake between 6-10% total energy intake, to 50% for both fatty acids in those with severe CRI. Of those with 'normal' renal function, 14% reported saturated fat intakes and 26% polyunsaturated fat intakes that fell within these recommendations. The median and interquartile ranges for fatty acid intakes are illustrated in Table 5.2.10. The median total fat and saturated fat intakes were significantly lower in those with severe CRI compared to those with 'normal' renal function. No significant differences between groups were observed for intake of unsaturated fats. Only one child with mild and one with severe CRI had sugar intakes that were equal to or below the recommended 10% total energy intake. In contrast, 11% with 'normal' renal function, 17% with mild, 26% with moderate and 22% with severe CRI had sugar intakes that formed ≥ 30% total energy intake. Despite this, the median total carbohydrate intake was significantly higher, and sugar intake significantly lower in those with severe CRI compared to 'normal' (Table 5.2.10).

Sodium

Individual intakes of sodium, and vitamin and minerals are illustrated in tables 5.2.11-5.2.14 (appendix 2). A substantial proportion of children in all groups had sodium intakes that exceeded the recommended maximum of 100 mmol/d, ranging from 42% of children with moderate CRI to 63% in children with 'normal' renal function. No significant differences were observed in median sodium intake between groups, when expressed either as a total daily intake or per kg body weight (Table 5.2.15). A significant correlation was observed between total sodium intake and energy intake for all groups (Figure 5.2.2), where 50% of the variation in sodium intake could be associated with total energy intake. Sodium intake did not significantly correlate with either systolic or diastolic blood pressure.

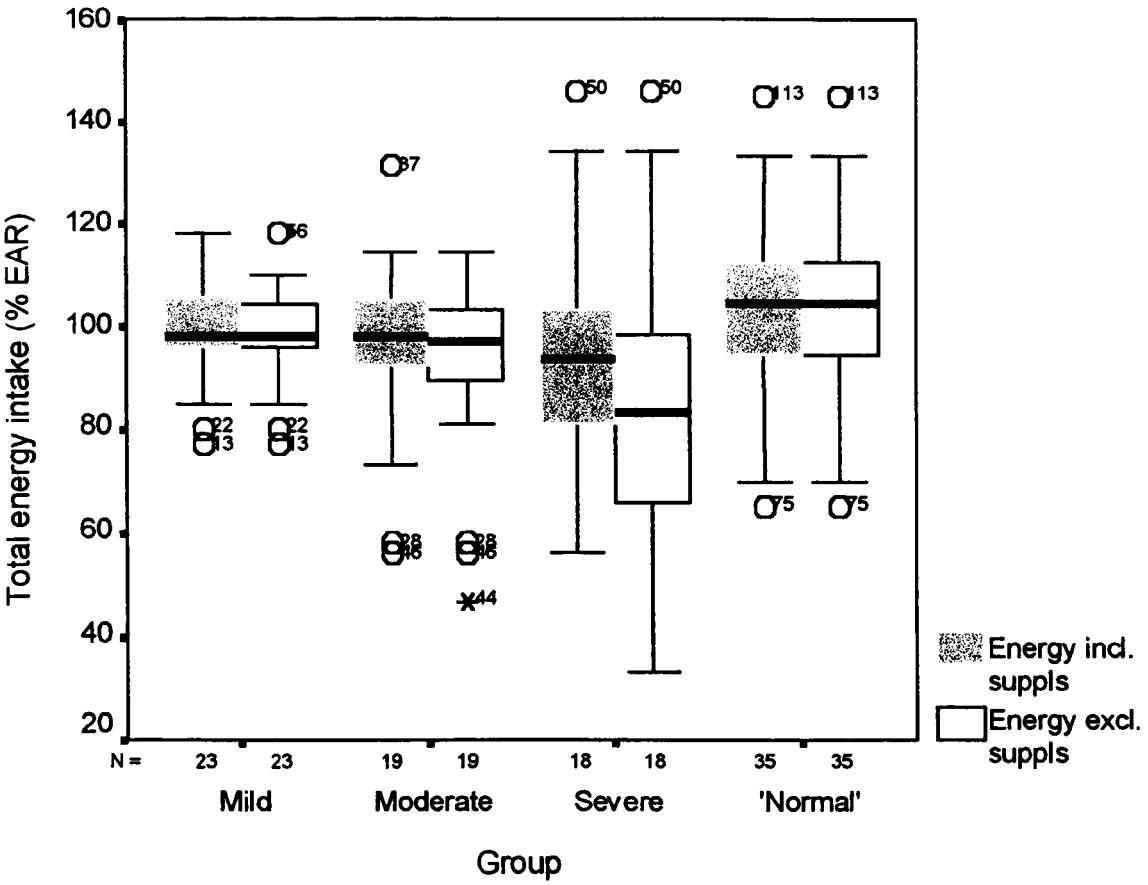
Calcium and phosphate

The proportion of children with calcium intakes ≤ 80% RNI increased with worsening severity of renal failure, increasing from 3% of children with 'normal' renal function to 9% with mild, 16% with moderate and 67% of children with severe CRI. Median calcium intake was significantly lower in the severe group compared to 'normal' (Table 5.2.15, Figure 5.2.3). The data, particularly in those with severe CRI were highly skewed with a number of outliers, such that the mean intake did not fall below the RNI for calcium (103%), whereas the median intake was only 74% RNI. Approximately 50% of children in each of the 'normal', mild and moderate groups had phosphate intakes that exceeded the maximum 1000mg/d recommended for children with renal failure, whereas only 28% children with severe CRI exceeded this value. The median phosphate intake was significantly lower in the severe group (Table 5.2.15, Figure 5.2.4), in line with dietetic advice.

Iron, folate and vitamin C

A substantial proportion of children in each of the groups had intakes of iron that were ≤ 80% RNI (in 20% of children with 'normal' renal function, 35% with mild, 37% with moderate and 50% with severe CRI). Folate intakes were lower in children with moderate and severe CRI compared to the other 2 groups, with 26% and 44% of children respectively having folate intakes ≤ 80% RNI, compared with 13% in the other 2 groups. Only 9% of children with 'normal' renal function had a vitamin C intake ≤ 80% RNI, whereas 26% of children with mild CRI had intakes below that recommended. Sixteen percent of children with moderate and severe CRI had potentially suboptimal intakes. Median dietary iron and folate intakes were significantly lower in the severe group compared to those with 'normal' renal function, whereas vitamin C intake from diet was significantly lower in those with mild CRI compared to 'normal'. Vitamin preparations were taken by a proportion of children in each group (Table 3.3.5-3.3.7). One child (2%) in the 'normal' group was taking an 'over the counter' (OTC) combined fat and water soluble vitamin preparation, whereas 20% of children with mild CRI were in receipt of a micronutrient supplement (predominantly an OTC preparation). A similar number of children with moderate CRI and 47% of children with severe CRI were in receipt of a vitamin supplement, although this was predominantly a water soluble preparation [Ketovite tablets (Paines & Byrne Ltd, West Byfleet, Surrey)], prescribed following dietary assessment.

Figure 5.2.1 Comparison of energy intakes in relation to severity of CRI



	Mild	Moderate	Severe	'Normal'
Energy (%EAR) + suppl				
Median	98	98	94	104
Interquartile range	95-106	90-106	81-104	93-112
P=				
Energy (%EAR) - suppl				
Median	98	97	83	104
Interquartile range	95-106	89-104	66-99	93-112
P=			0.003	

EAR, estimated average requirement; suppl, nutritional supplement
P value is given for comparison of groups with 'normal', derived from the Kruskal-Wallis and two sample Mann-Whitney U-test. P <0.05 was deemed to be significant

Table 5.2.5 Comparison of other measures of energy intake and protein intakes in relation to severity of CRI

Nutrient (Median and interquartile range)	**'Normal'** (n=35)	**Mild** (n=23)	**Moderate** (n=19)	**Severe** (n=18)
Energy (- suppl) (kcal/kg)	69 56 to 84	71 56 to 86	61 45 to 94	53 * 42 to 68
Energy (+ suppl) (kcal/kg)	69 56 to 84	71 56 to 86	70 45 to 94	59 47 to 92
Protein [as % energy (+ suppl)]	13.1 11.9 to 14.5	12.4 11.1 to 13.8	12.7 11.3 to 14.4	11.6 ** 8.1 to 12.0
Protein [as % energy (- suppl)]	13.1 11.9 to 14.5	12.4 11.1 to 13.8	12.7 11.3 to 14.4	12.0 10.7 to 13.2
Protein (g/kg)	2.3 1.7 to 2.9	2.2 1.5 to 2.9	2.1 1.5 to 2.8	1.7 1.4 to 3.0

EAR, expected average requirement; suppl, nutritional supplement
p value is given for comparison of groups with 'normal', * $p = 0.042$, ** $p = 0.001$

Table 5.2.10 Comparison of fat and carbohydrate intakes (inclusive of supplements) in relation to severity of CRI

Nutrient (Median and interquartile range)	**'Normal'** (n=35)	**Mild** (n=23)	**Moderate** (n=19)	**Severe** (n=18)
Total fat (% energy)	36.7 34.0 to 40.0	36.0 32.2 to 37.9	35.0 31.6 to 40.2	33.9 * 29.2 to 36.7
Saturated fat (% energy)	14.3 12.7 to 15.7	15.1 12.0 to 17.2	13.8 12.1 to 16.4	11.2 * 9.1to 13.9
Mono-unsaturated fat (% energy)	11.1 10.2 to 13.2	11.1 9.4 to 12.5	10.5 7.5 to 14.1	10.2 8.1 to 11.9
Poly-unstaurated fat (% energy)	4.9 4.1 to 7.0	4.4 3.7 to 5.5	5.0 3.6 to 5.8	5.65 3.6 to 6.5
Carbohydrate (% energy)	50.6 47.0 to 52.1	50.7 47.9 to 55.7	52.7 43.2 to 55.0	54.8 *** 48.9 to 60.6
Sugar (% energy)	25.5 21.9 to 27.9	25.0 20.0 to 28.3	25.2 17.7 to 30.7	20.0 ** 16.1 to 24.7

EAR, expected average requirement; RNI, recommended nutrient intake
p value is given for comparison of groups with 'normal', * $p = 0.036$, ** $p = 0.029$, *** $p = 0.011$

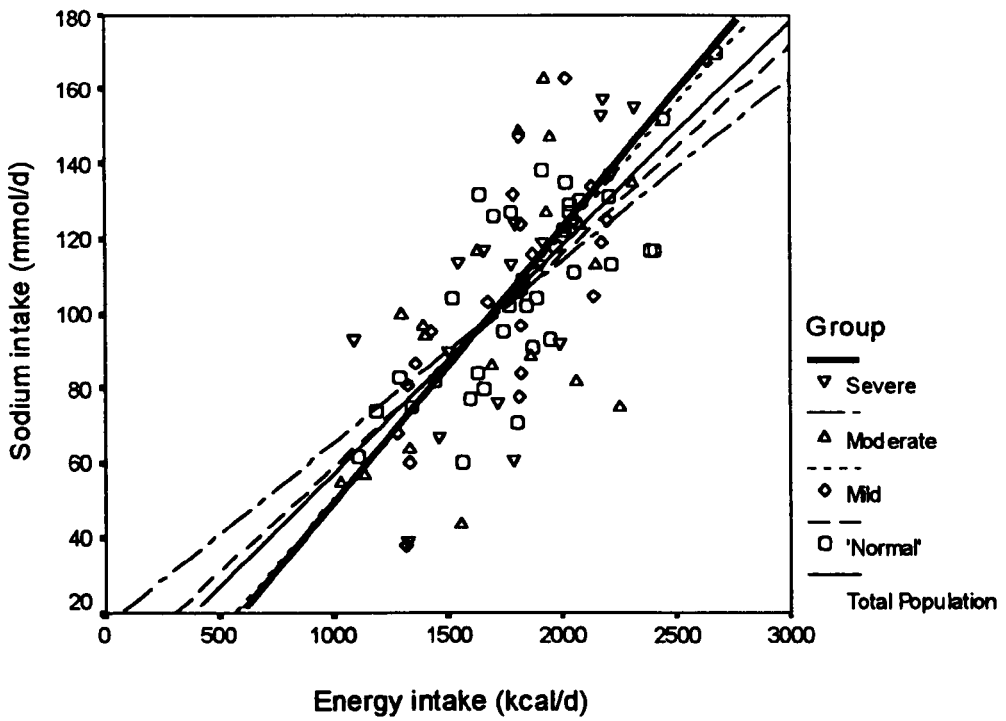
Table 5.2.15 Comparison of sodium and vitamin & mineral intakes (inclusive of nutritional supplements, micronutrients excluded) in relation to severity of CRI

Nutrient (Median and interquartile range)	**'Normal'** (n=35)	**Mild** (n=23)	**Moderate** (n=19)	**Severe** (n=18)
Total sodium (mmol)	109 83 to 127	105 84 to 124	97 75 to 127	114 87 to 141
Sodium (mmol/kg)	4.2 2.9 to 4.9	4.2 3.0 to 4.7	3.8 2.8 to 5.8	3.5 2.5 to 5.7
Calcium (% RNI)	159 108 to 198	132 104 to 190	120 89 to 190	74 ***** 67 to 105
Phosphate (mg)	990 871 to 1215	989 820 to 1182	983 709 to 1220	845 **** 612 to 1066
Iron (% RNI)	105 82 to 128	91 71 to 122	93 56 to 112	79 ** 47 to 105
Folate (% RNI)	152 102 to 190	137 88 to 178	128 73 to 188	81 *** 59 to 134
Vitamin C (% RNI)	209 135 to 296	122 * 76 to 206	179 108 to 300	165 109 to 246

RNI, reference nutrient intake

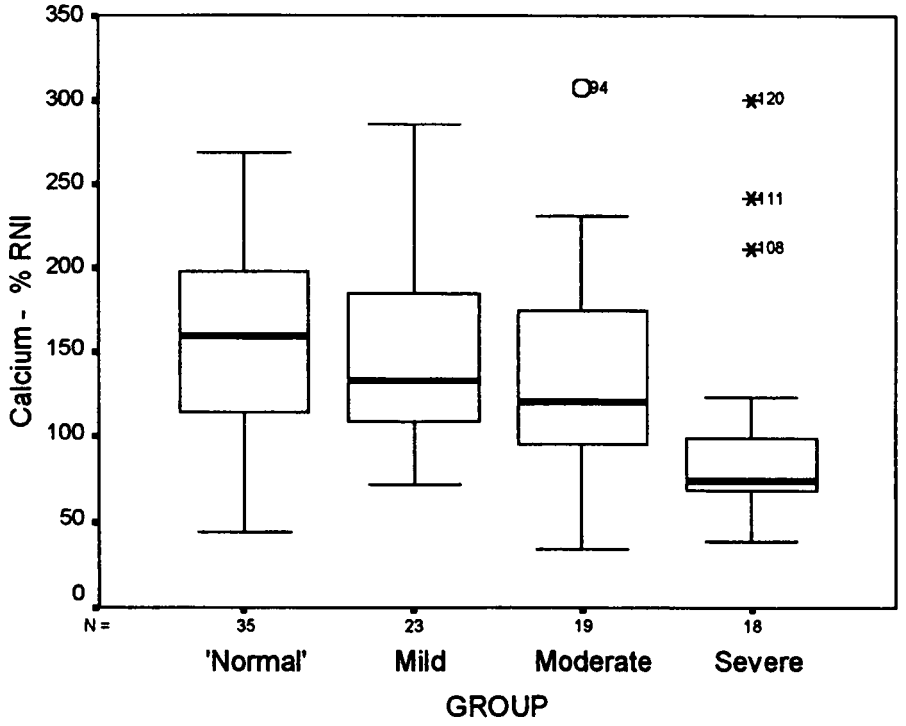
p value is given for comparison of groups with 'normal', * p = 0.037, ** p = 0.027, *** p = 0.012, **** p = 0.008, ***** p = 0.001

Figure 5.2.2 Correlation between total energy and sodium intakes in relation to severity of CRI



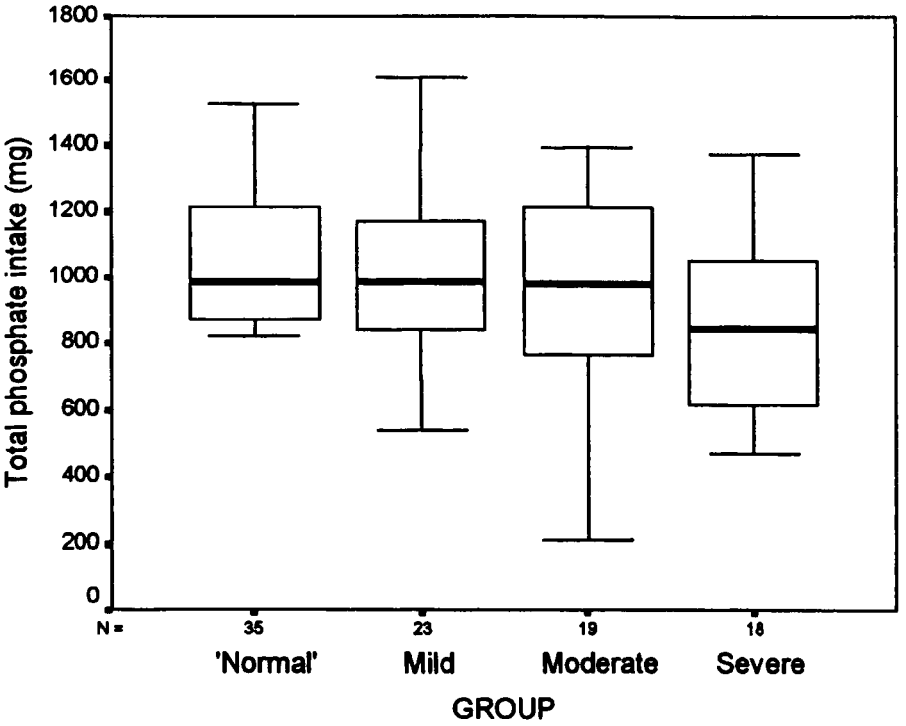
Total	[R^2=0.50; F=93.76; 1,93df, P<0.0001]
'Normal'	[R^2=0.59; F=47.86; 1,33df, P<0.0001]
Mild CRI	[R^2=0.54; F=24.34; 1,21df, P<0.0001]
Moderate CRI	[R^2=0.30; F=7.20; 1,17df, P=0.016]
Severe CRI	[R^2=0.61; F=24.74; 1,16df, P<0.0001]

Figure 5.2.3 Comparison of calcium intakes in relation to severity of CRI



Note: RNI was used for comparison as there are no recommendations for calcium intake in children with CRI

Figure 5.2.4 Comparison of phosphate intakes in relation to severity of CRI



Note: Total phosphate (mg) was used for comparison against recommendations made for children with CRI.

5.3 Biochemical variables

Urea and electrolytes

Plasma concentration of electrolytes and metabolites for each individual within each group are illustrated in tables 5.3.1-5.3.4 (appendix 2). No child had a plasma potassium concentration that exceeded 5.5 mmol/l. Two children with 'normal' renal function and one child in both the mild and moderate groups had plasma bicarbonate concentrations less than 18 mmol/l, whereas 5 children (26%) with severe CRI were found to have low concentrations. Although five children were in receipt of sodium bicarbonate, 4 of the 5 children with low bicarbonate concentrations were not in receipt of such a medication (table 3.3.7). Table 5.3.5 illustrates the median and interquartile range for plasma concentrations of electrolytes and metabolites that are routinely monitored in children with CRI. No significant differences were observed for plasma sodium concentrations between groups. The median plasma potassium was significantly higher in those with severe CRI compared to those with 'normal' renal function, although the median and interquartile range was within the normal reference range. Conversely, the median plasma bicarbonate was significantly lower in those with severe CRI compared to those in the 'normal' group and the bottom of the interquartile range was outside the normal reference range, despite treatment in some with sodium bicarbonate. Median plasma urea and creatinine concentrations were significantly elevated in all groups of children with CRI compared to 'normal', increasing exponentially with increasing severity of CRI.

Bone-related variables

Individual plasma concentrations for variables relating to bone activity are depicted in tables 5.3.6-5.3.9 (appendix 2). No child with 'normal' renal function or moderate CRI had a plasma phosphate concentration that exceeded 1.7 mmol/l, whereas 2 children with mild and 3 children with severe CRI did. Those with mild CRI were both over 5 years of age and did not have high dietary intakes of phosphate (869 & 820 mg/d) (Table 5.2.11, appendix 2). There was no clear pattern either in those with severe CRI with high phosphate concentrations, with only one of the 3 children having a high phosphate intake, and this child was not one of those in receipt of a phosphate binder (Table 3.3.7). Only one of the children with a phosphate intake above 1000mg/d was receiving a prescribed phosphate binder. Median and interquartile ranges for plasma concentrations of variables relating to bone activity in relation to severity of CRI are

illustrated in Table 5.3.10. Serum PTH and phosphate concentrations in each group are also depicted in Figures 5.3.1 and 5.3.2 respectively. Despite medical and dietetic intervention, median plasma phosphate concentration was significantly higher in children with severe CRI compared to those with 'normal' kidney function, although the interquartile range was within the normal laboratory reference range for mean age of the study population (1.0-1.7 mmol/l). Plasma calcium concentrations did not drop significantly and plasma alkaline phosphatase did not increase significantly across the groups. Median serum PTH concentration however, increased significantly in children with both moderate and severe CRI compared to 'normal', although the data was highly skewed. In those with moderate CRI, the mean and SD (68 $\pm$ 56 ng/l), median and interquartile range for PTH concentration were within our normal adult reference range (12-72 ng/l), albeit at the upper end of the range. In the severe group, the mean and SD (158 $\pm$ 162), median and interquartile range exceeded our reference range.

Plasma proteins

Individual concentrations of plasma markers of protein status are depicted in tables 5.3.11-5.3.14 (appendix 2). Two children with 'normal' renal function and mild CRI had plasma albumin concentrations that were $\leq$ 35g/l, as determined by the BCP method. On the other hand, 7 children with both moderate and severe CRI had suboptimal plasma albumin concentrations. Only two of the 7 children with moderate CRI had significant proteinuria (table 3.3.2) whereas all but one of the 7 children with low plasma albumin concentrations in the severe group had significant proteinuria. Median plasma albumin, as measured by the BCP method, was significantly lower in children with both moderate and severe renal failure compared to 'normal' (Table 5.3.15). Significant differences in plasma albumin were no longer observed when those with a urinary protein to creatinine ratio of 0.1g/ mmol or more were excluded. Plasma albumin, as measured by the ITM method did not differ significantly between the groups, whether the degree of proteinuria was accounted for or not. Plasma albumin concentration measured by both the usual BCP method and the investigative ITM method were not suitable for comparison by Bland and Altman (1986) plots between the groups at baseline, due to the small number of children involved. This comparison was therefore conducted from all data obtained over the two-year period, acknowledging that the results involved repeated measurements on the same individuals (Section 6.8).

Median plasma prealbumin was noted to be significantly higher in children with both moderate and severe CRI compared to those with 'normal' renal function (Table 5.3.15). Linear regression revealed a significant inverse relationship between plasma prealbumin concentrations and GFR, with approximately 11% of the variation in prealbumin being attributed to GFR (Figure 5.3.3). Plasma prealbumin concentrations appeared to increase with age, although the association was much weaker than for GFR (Figure 5.3.4).

Lipids

Tables 5.3.16-5.3.19 (appendix 2) depict serum lipid concentrations in children with varying degrees of renal failure and with 'normal' renal function. Over a quarter of children in each group had serum cholesterol concentrations greater than 5 mmol/l. Few children had a HDL cholesterol concentration below 1 mmol/l, although 3 children with severe CRI and 5 children with 'normal' renal function did have low concentrations. Although the samples were obtained in the non-fasted state, only 2% of children in the 'normal' group had triglyceride concentrations that exceeded 2 mmol/l, whereas 32% of children with severe CRI had higher than normal concentrations. Children with moderate CRI appeared to have significantly higher serum cholesterol concentrations when compared to 'normal' than the other groups of CRI (Table 5.3.20). When serum HDL concentrations were taken into consideration however, it was only those with severe CRI that exhibited a significantly higher total: HDL cholesterol ratio compared to children with 'normal' kidney function (Figure 5.3.5). Serum triglyceride concentrations increased with deteriorating renal function, becoming significantly different to 'normal' in those with both moderate and severe CRI (Figure 5.3.6).

Anaemia-related variables

Individual plasma variables relating to iron status are illustrated in tables 5.3.21-5.3.24 (appendix 2). Haemoglobin concentrations were significantly lower in those with severe CRI compared to 'normal' (Table 5.3.25), with four children with severe CRI exhibiting a haemoglobin of less than 10 g/dl. Children with severe CRI exhibited significantly higher plasma ferritin concentrations compared to those with 'normal' renal function, with 4 children having a plasma ferritin of > 100 μg/l. No differences were observed in percentage hypochromic cell values across the groups, with only one child with mild CRI and one with 'normal' renal function exhibiting a value of greater than 10%.

Table 5.3.5 Comparison of plasma concentrations of relevant electrolytes and metabolites in relation to severity of CRI

Variable (Median and interquartile range)	**'Normal'** (n=58)	**Mild** (n=27)	**Moderate** (n=21)	**Severe** (n=19)
Sodium (mmol/l)	139 137 to 140	138 137 to 140	138 138 to 140	140 138 to 141
Potassium (mmol/l)	4.0 3.7 to 4.2	4.1 3.7 to 4.4	4.1 3.7 to 4.4	4.5 ** 3.8 to 4.8
Bicarbonate (mmol/l)	23 22 to 25	23 20 to 24	23 21 to 24	20 *** 17 to 23
Urea (mmol/l)	4.9 4.4 to 5.7	5.8 * 4.7 to 7.1	8.5 **** 6.6 to 11.0	17.0 **** 14.4 to 18.1
Creatinine (μmol/l)	51 46 to 60	66 **** 55 to 83	107 **** 87 to 129	202 **** 152 to 301

p value is given for comparison of groups with 'normal', * $p = 0.018$, ** $p = 0.013$, *** $p = 0.003$, **** $p < 0.001$

Table 5.3.10 Comparison of plasma concentrations of variables relating to bone activity in relation to severity of CRI

Plasma/ serum variable (Median and interquartile range)	**'Normal'** (n=58)	**Mild** (n=27)	**Moderate** (n=21)	**Severe** (n=19)
Calcium (mmol/l)	2.44 2.35 to 2.49	2.46 2.39 to 2.51	2.43 2.37 to 2.48	2.38 2.24 to 2.46
Phosphate (mmol/l)	1.40 1.26 to 1.49	1.35 1.23 to 1.49	1.41 1.34 to 1.52	1.50 * 1.40 to 1.60
Alkaline phosphatase (mmol/l)	507 442 to 595	519 428 to 596	536 399 to 679	620 403 to 764
PTH (ng/l)	18 12 to 29	21 13 to 34	57 ** 38 to 71	99 ** 57 to 186

p value is given for comparison of groups with 'normal', * $p = 0.002$, ** $p < 0.001$

Phosphate reference range 1.0-1.7 mmol/l; PTH reference range 12-72 ng/l

Figure 5.3.1 Serum PTH concentrations in relation to severity of CRI

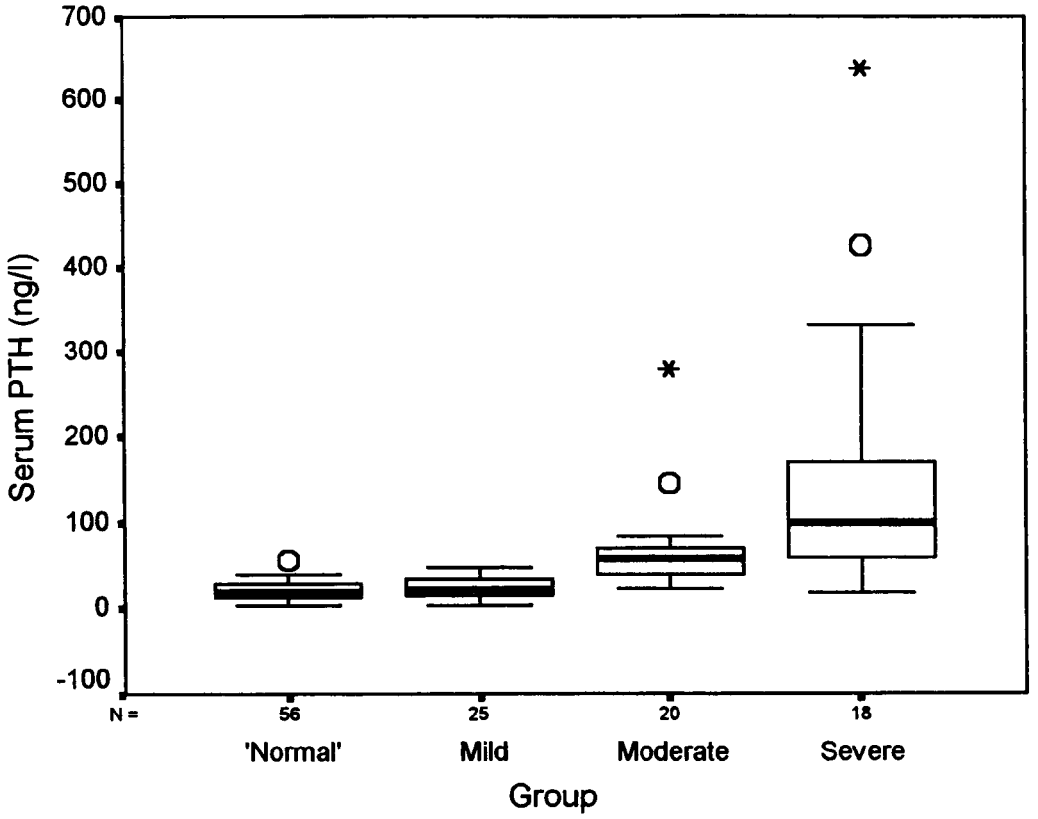


Figure 5.3.2 Plasma phosphate concentrations in relation to severity of CRI

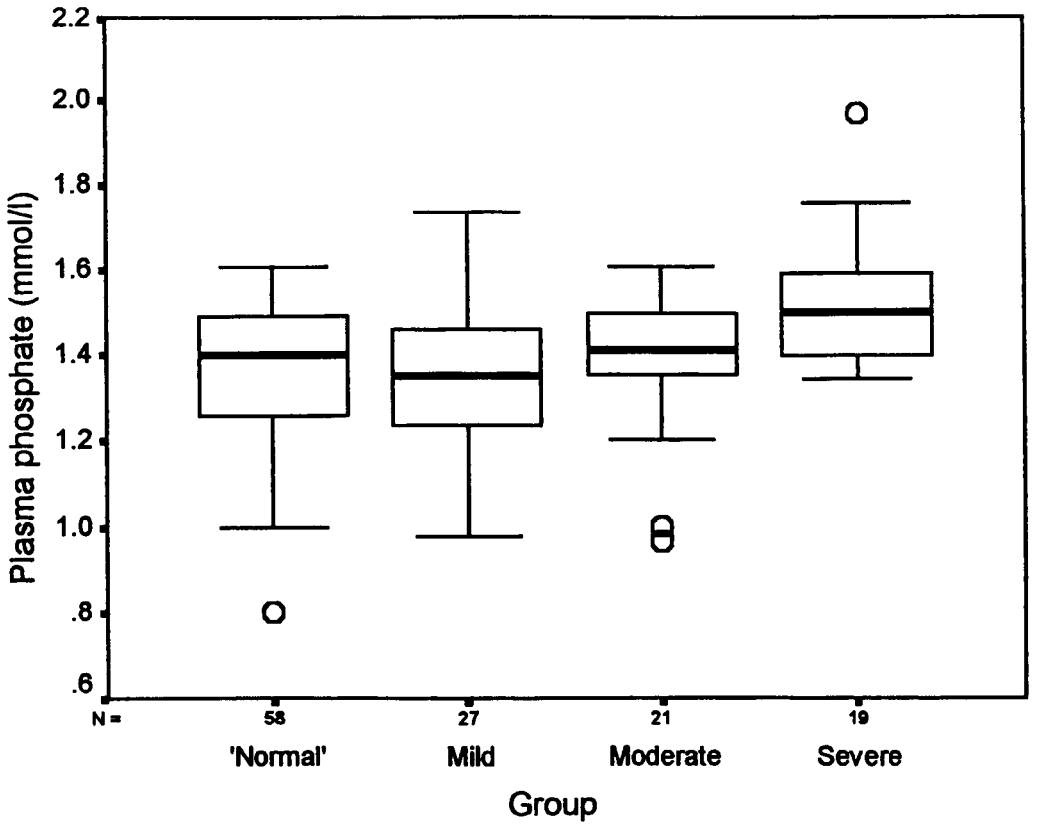


Table 5.3.15 Comparison of markers of protein status in relation to severity of CRI

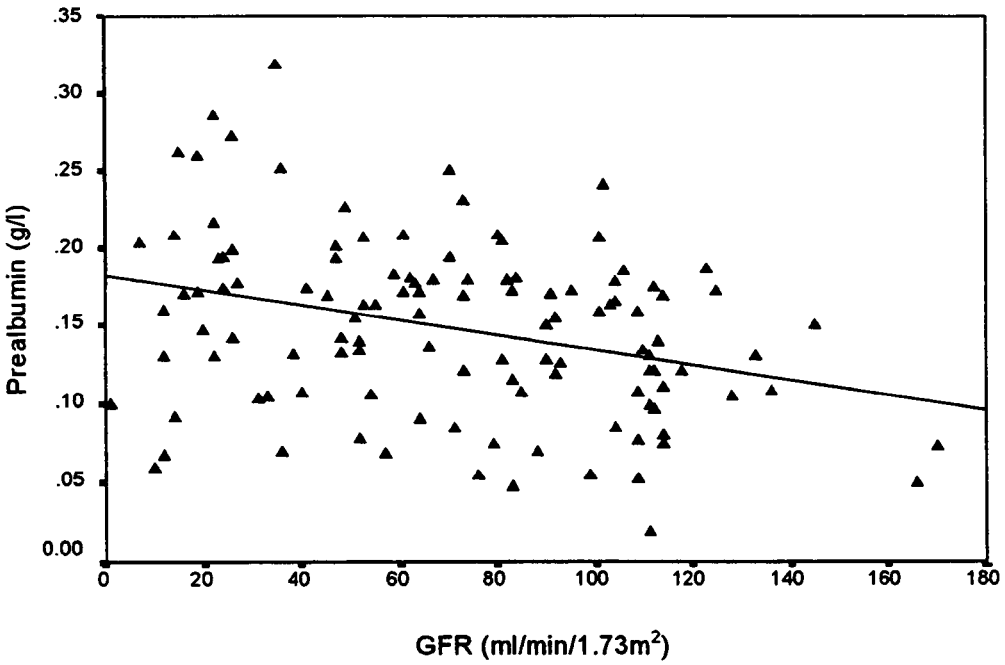
Variables (Median and interquartile range)	**'Normal'** (n=58)[$]	**Mild** (n=27)[$]	**Moderate** (n=21)[$]	**Severe** (n=19)[$]
Urine protein: creatinine (g/mmol)	0.01 0.01 to 0.01	0.01 0.01 to 0.02	0.04 ***** 0.02 to 0.20	0.12 ***** 0.08 to 0.26
Plasma albumin (g/l) (BCP method)	40 38 to 41	40 38 to 41	39 * 35 to 40	36 **** 34 to 39
Plasma albumin (g/l) [#] – if proteinuria < 0.1g/mmol (n=)	40 38 to 41 54	39 38 to 41 25	39 37 to 41 13	39 36 to 41 7
Plasma albumin (g/l) (ITM method)	39 35 to 41	40 36 to 42	38 34 to 41	37 34 to 40
Plasma albumin (g/l) [+] – if proteinuria < 0.1g/mmol (n=)	39 35 to 41 54	40 36 to 42 25	38 32 to 42 13	40 35 to 42 7
Plasma prealbumin (g/l)	0.13 0.01 to 0.17	0.17 0.13 to 0.18	0.17 ** 0.13 to 0.21	0.17 *** 0.13 to 0.21

[#] BCP (bromocresol purple) method; [+] ITM (immunoturbidometric) method

[$]Total number except where n is specified excluding those with substantial proteinuria (i.e. only those with proteinuria < 0.1g/ mmol)

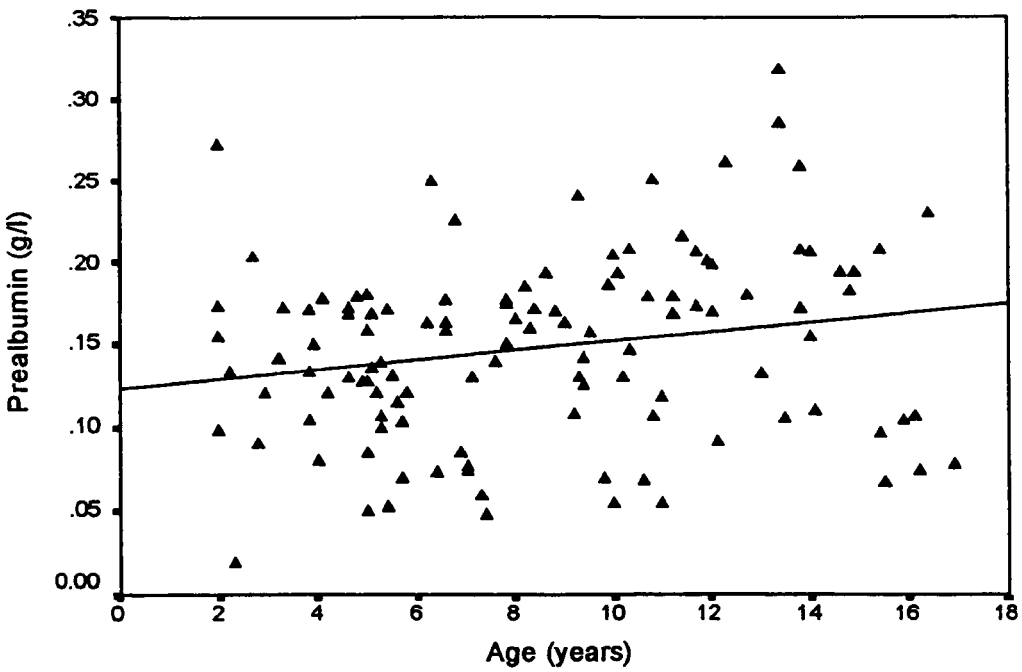
p value is given for comparison of groups with 'normal', * p = 0.025, ** p = 0.018,*** p = 0.016, **** p = 0.001, ***** p < 0.001

Figure 5.3.3 Plasma prealbumin concentrations in relation to GFR



$Y = -0.0005x + 0.182$ [R^2=0.11; F=13.61; 1,115df, P<0.0001]

Figure 5.3.4 Plasma prealbumin concentrations in relation to age



$Y = 0.003x + 0.125$ [R^2=0.04; F=4.7; 1,115df, P=0.032]

Table 5.3.20 Comparison of serum lipid concentrations in relation to severity of CRI

Serum variable (Median and interquartile range)	**'Normal'** (n=57)	**Mild** (n=24)	**Moderate** (n=21)	**Severe** (n=18)
Total cholesterol (mmol/l)	4.5 4.0 to 5.2	4.7 4.1 to 5.6	5.2 * 4.7 to 6.1	5.0 4.4 to 5.6
Total cholesterol (mmol/l) – no significant proteinuria [+] **n=**	4.5 4.0 to 5.2 53	4.6 4.1 to 5.5 20	5.0 4.4 to 6.1 12	5.3 4.6 to 5.6 6
HDL cholesterol (mmol/l)	1.4 1.3 to 1.7	1.5 1.1 to 1.7	1.6 1.2 to 1.7	1.3 1.1 to 1.6
Total cholesterol: HDL cholesterol	3.1 2.7 to 3.6	3.5 2.9 to 4.3	3.6 2.9 to 4.1	4.2 ** 2.8 to 4.9
Total cholesterol: HDL cholesterol [+] **n=**	3.1 2.7 to 3.5 50	3.5 2.9 to 4.3 19	3.5 2.8 to 4.1 11	4.1 2.5 to 5.1 6
Triglycerides (mmol/l)	0.9 0.6 to 1.4	1.0 0.8 to 1.4	1.3 *** 1.0 to 1.8	1.5 *** 1.1 to 2.6

[+] included if proteinuria < 0.1g/mmol – total value of n denoted as lower than for whole group
p value is given for comparison of groups with 'normal', * p = 0.027, ** p = 0.023, *** p = 0.001

Figure 5.3.5 Serum total: HDL cholesterol ratio in relation to severity of CRI

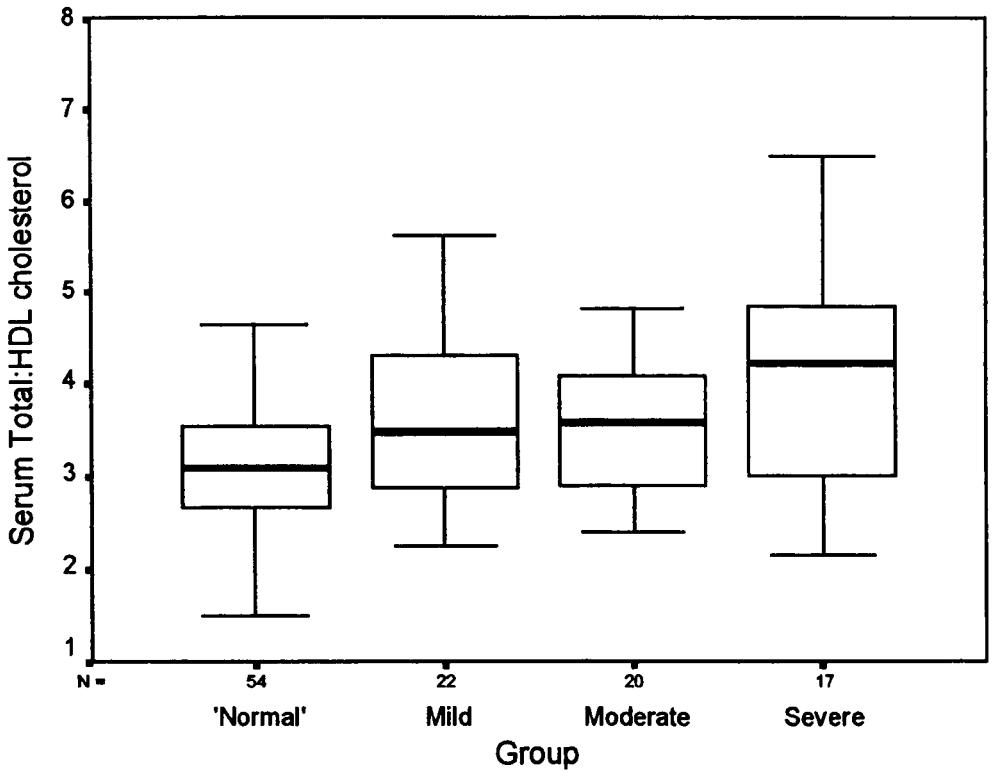


Figure 5.3.6 Serum triglycerides in relation to severity of CRI

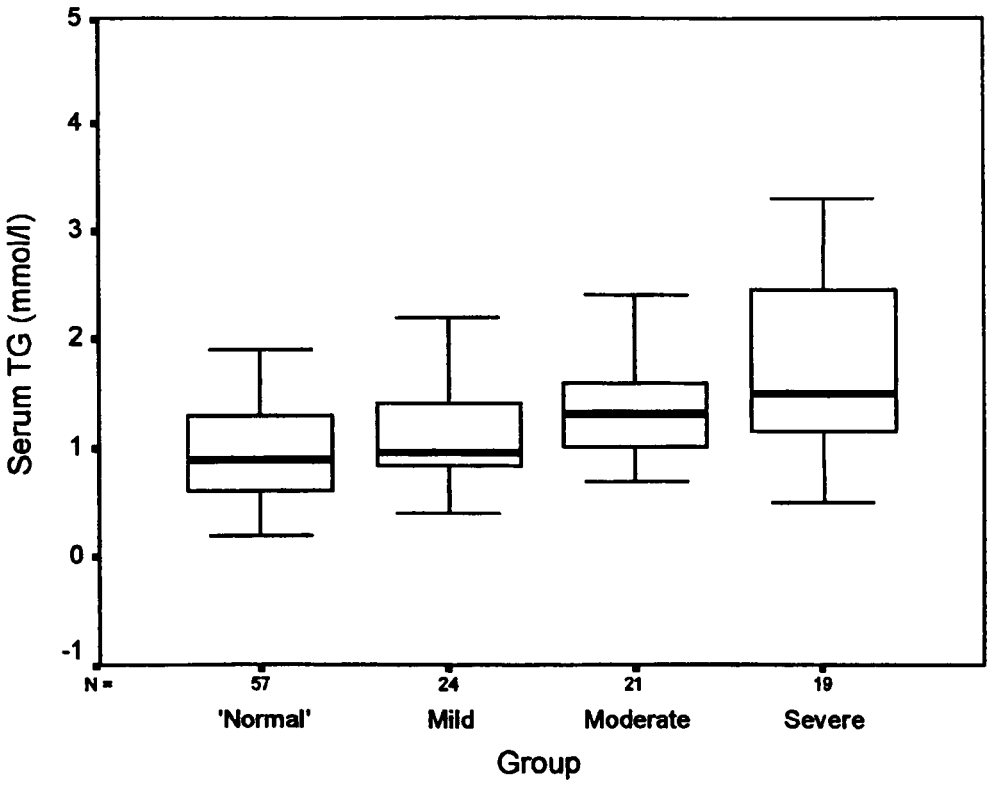


Table 5.3.25 Comparison of plasma iron-related variables in relation to severity of CRI

Plasma variable (Median and interquartile range)	**'Normal'** (n=55)	**Mild** (n=25)	**Moderate** (n=19)	**Severe** (n=18)
Haemoglobin (g/ dl)	12.4 11.9 to 12.9	12.7 12.0to 13.8	12.7 12.0 to 14.1	11.4 ** 10.0 to 12.2
% Hypochromic cells	0.7 0.4 to 1.4	1.2 0.5 to 2.9	1.1 0.4 to 1.9	1.3 0.5 to 3.2
Ferritin (µg/l)	25 18 to 38	23 18 to 35	31 21 to 41	40 * 23 to 84

p value is given for comparison of groups with 'normal', * $p = 0.031$, ** $p < 0.001$

Chapter Six

LONGITUDINAL RESULTS AND DISCUSSION OF INDIVIDUALS

Longitudinal results involved observing differences in anthropometric indices, blood pressure, nutritional intakes and biochemical parameters over a 2 year period in children with a degree of chronic renal insufficiency. Due to ethical considerations involving unnecessary additional monitoring, including invasive procedures such as blood tests, children with 'normal' renal function did not form part of the longitudinal cohort. Changes in each variable over time compared to baseline were calculated for each individual, and comparisons were subsequently made between the groups of CRI, using UNIANOVA. To enable associations between variables to be placed into context, discussion of the progress of individuals was included, thereby accounting for the heterogeneity of the sample population in relation to covariates such as age and underlying diagnosis, and allowing for the individual approach employed by medical and dietetic practitioners. The order in which the sections in this chapter are dealt with is a little out of keeping with the other chapters, due to the importance of keeping some nutrients together, such as energy and protein in relation to growth. It was felt that energy, protein intake and growth were three of the most important outcome measures, and were therefore addressed first. Sodium is discussed in relation to hypertension, yet the individual data forms part of the tables along with calcium and phosphate, as it would not be practical to produce a table for one nutrient alone.

6.1 Patients

Demographic data for those children with CRI who formed part of the longitudinal study are depicted in Tables 6.1.1-6.1.3. There were two less children with mild CRI at the start of the longitudinal series compared to that reported for baseline, due to transfer of one girl (2) to the adult renal unit following the EDTA GFR, and exclusion of one boy (3) due to unreliable nutritional intake data and poor clinic attendance.

Six girls with mild CRI failed to complete the 2-year study; three withdrew from the study, two moved to other regions in the UK and one was transferred to the adult renal unit one year into the study. Two boys with moderate CRI failed to complete the 2-year follow up, one being due to unwillingness to complete food diaries and the other exhibited such a rapid decline in renal function that he commenced dialysis one year into the study. Six children (5 boys) with severe CRI failed to complete 2 years of the study. All six children reached end stage renal disease, of which 4 children entered onto the peritoneal dialysis programme and 2 children received pre-emptive transplants.

Children with severe CRI were older by a mean of approximately 2 years compared to those with mild and moderate CRI. At baseline, 6 children with mild CRI, 4 with moderate and 3 with severe CRI were under 5 years of age. By the end of the 2-year period, only 2 children with mild, 1 with moderate and 1 with severe CRI remained under 5 years of age. Two children entered the dialysis programme in this age group, one from the moderate and one from the severe group. The number of children within the age-band 5-9 years remained fairly constant over the 2 year period, although there were twice as many children falling into this band within the mild and moderate groups, compared to those with severe CRI. A greater proportion of children in the latter group fell into the 10 - <13 year age band, which explains the majority of difference in mean ages between the groups. By the end of the 2 years however, there were only 3 children in each group remaining in the 10 - < 13 age band. Three of the four children with severe CRI who left this age band, entered onto the ESRD programme. The numbers of children within each group falling into the age bands 13-<16 years and 16 years and above were similar at baseline. The balance in age changed over the 2 year period, such that by the end of the study, there were more children in the 13-<16 year age band with moderate CRI, and more children aged 16 years and above in the severe group. Those with mild CRI tend to be transferred to adult follow up at an earlier age than children with more advanced renal failure, thereby reducing the maximum age at completion of the study (16.7 yrs age) compared to those with moderate (18.7 yrs) and severe CRI (18 yrs age).

Children that failed to complete the 2 year period could be compared at baseline with those that did complete the study, to determine whether there were any variables that may be associated with completion and/ or progression of CRI, and whether there were

any differences between the 2 groups that could affect results of the longitudinal study (Table 6.1.4). Mean age was similar for children with severe CRI, irrespective of whether they did or did not complete the study. Children with mild CRI who did not complete the study had a mean age higher than those who did, with the oldest child having been transferred to an adult unit. The youngest children were not those to have been withdrawn by parents from the study. In children with moderate CRI however, the two failing to complete the study were two of the youngest, so that the mean age at baseline in those who completed the study was higher than for the group as a whole. There were no obvious patterns between those who did or did not complete the study based on primary diagnosis. There was little difference in height or BMI SDS for children with mild CRI between those who completed the 2-year study or not. The two children with moderate CRI who did not complete the study however, both had below average height and BMI SDS's, the mean being substantially below the mean for the remainder of the group. Despite this, the mean for the remainder of the children with moderate CRI who completed the study was not substantially above the mean for the whole group (Table 5.1.5). For children with severe CRI, there was little difference in height SDS between those who completed the study or not. BMI SDS however, was higher in the children who failed to complete the study, although the mean BMI SDS for the whole group was not substantially different from the mean for those who completed the 2 years.

Systolic blood pressure SDS did not vary between children with mild CRI who did or did not complete the study. Unfortunately, it was not possible to determine this for the children with moderate CRI who failed to complete 2 years, due to their height not being great enough to calculate SDS's. Children with severe CRI who did not complete the study exhibited almost double the mean SDS for SBP compared with those who remained in the study (Table 6.1.4). This did have an impact on the overall mean SBP SDS, where the children who completed the study had a lower mean SBP SDS than that described for the group as a whole (Fig 5.1.3). A similar pattern also emerged for DBP, which was also seen in children with mild CRI, although the means for both the overall groups were not so different from the means for just the children completing the study. The protein: creatinine ratio was similar for children with mild CRI who did or did not complete the study. This however, was not the case for children in the other 2 groups of CRI. The child with moderate CRI who progressed onto dialysis had the highest degree

of proteinuria within the group, whereas the child who withdrew from the study did not have proteinuria. All 6 children with severe CRI who reached ESRD had substantial proteinuria, the mean being twice that of those with severe CRI who completed the study.

The prescription of medical and dietetic therapies for each child over the 2-year period is depicted in tables 6.1.5-6.1.7. Table 6.1.8 compares changes in the number of children prescribed various therapies between the groups of CRI at baseline, one and 2 years. The most notable changes during the two year period include the increased prescription of Ketovite tablets (water soluble vitamins) in those with moderate and severe CRI and the reduction of vitamin supplement usage in those with mild CRI. One Ketovite tablet contains 16.6 mg vitamin C, 1 mg riboflavin, 1mg thiamin, 330 μg pyridoxine, 3.3 mg nicotinamide, 1.2 mg pantothenate, 5 mg vitamin E, 170 μg biotin, 250 μg folic acid and 50 mg inositol. An increase in prescription of iron supplements was observed in children with moderate and severe CRI compared to baseline. Those with mild CRI tended to have a short course of iron supplementation, whereas those with moderate and severe CRI tended to remain on oral iron. In those with moderate CRI, a substantial increase in the number of children being prescribed a vitamin D analogue (alfacalcidol) was also noted, with little change in the prescription of calcium carbonate. Throughout the second half of the study, all but one child with severe CRI was in receipt of alfacalcidol. There was a small increase in the prescription of ACE inhibitors in those with mild and moderate CRI during the study period.

Table 6.1.1 Longitudinal demographic data of children classified at baseline with mild CRI, at the time that they left the study

Patient number	Sex (M/F)	Age (yrs)	Change in estimated GFR	Protein: creatinine (g/mmol)	Time point on leaving the study *	Reason for leaving study
1	M	5.9	0	0.01	4	C
4	M	7.5	-19	0.02	4	C
5	F	4.2		0.01	0	M
6	F	4.7	-3	0.02	4	C
7	M	5.6	-2	0.01	4	C
8	M	6.8	-13	0.04	4	C
9	F	12.6	3	0.01	4	C
10	F	18	0	0.02	2	T
11	M	9.2	-11	0.01	4	C
12	F	14.8	-11	0.03	1	W
13	M	7.2	-21	0.01	4	C
14	M	11.2	-6	0.02	4	C
15	F	11.8	3	0.01	1	M
16	F	5.1		0.01	0	W
17	M	13.5	-15	0.01	4	C
18	M	12.1	-22	0.03	4	C
19	F	15.6	-23	0.01	4	C
20	M	15.9	-20	0.01	4	C
21	M	13.9	3	0.01	4	C
22	F	8.8	-6	0.02	2	W
23	F	16.7	-8	0.15	4	C
24	M	4.1	-1	0.60	4	C
25	F	8.7	4	0.01	4	C
26	M	9.8	-8	0.25	4	C
27	M	8.4	-2	0.01	4	C
Summary for 2yr data	74% M	10.0	-8.4	N=3 (16%)		C=19

* Time points, 0, baseline; 1, 6 months; 2, 1 year; 3, 18 months; 4, 2 years
C, completed the 2 year study; T, transfer to other unit; W, withdrew, M, moved

Summary for those completing the 2 year study
Means given for age and change in estimated GFR
Number and % of sample given for sex and protein: creatinine $\geq$ 0.1 g/ mmol (denotes substantial proteinuria)

Table 6.1.2 Longitudinal demographic data of children classified at baseline with moderate CRI, at the time that they left the study

Patient number	Sex (M/F)	Age (yrs)	Change in estimated GFR	Protein: creatinine (g/mmol)	Time point on leaving the study *	Reason for leaving study
28	M	14.3	-6	0.04	4	C
29	M	7.8	-4	0.11	4	C
30	F	18.7	-7	0.15	4	C
31	M	7.6	-4	0.02	4	C
32	M	17.8	-7	0.28	4	C
33	M	2.6	-2	0.01	1	W
34	F	5.3	-4	0.11	4	C
35	M	11.5	-12	0.16	4	C
36	M	3.3	-26	1.43	2	D
37	M	4.0	-9	0.24	4	C
38	M	11.5	-11	0.01	4	C
39	F	15.1	-5	0.01	4	C
40	M	13.1	-6	0.11	4	C
41	M	12.2	-8	0.01	4	C
42	M	15.4	-10	0.04	4	C
43	M	14.0	-3	0.17	4	C
44	F	7.9	4	0.01	4	C
45	M	9.4	-6	0.28	4	C
46	F	13.7	-12	0.49	4	C
47	M	8.9	6	0.04	4	C
48	M	7.2	1	0.01	4	C
Summary for 2yr data	74% M	11.3	-5.5	N=10 (53%)		C=19

*Time points: 0, baseline; 1, 6 months; 2, 1 year; 3, 18 months; 4, 2 years
C, completed the 2 year study; W, withdrew; D, dialysis

Summary for those completing the 2 year study
Means given for age and change in estimated GFR
Number and % of sample given for sex and protein: creatinine $\geq$ 0.1 g/ mmol (denotes substantial proteinuria)

Table 6.1.3 Longitudinal demographic data of children classified at baseline with severe CRI, at the time that they left the study

Patient number	Sex (M/F)	Age (yrs)	Change in estimated GFR	Protein: creatinine (g/mmol)	Time point on leaving the study *	Reason for leaving study
49	F	9.2	-8	0.03	4	C
50	M	6.9	-9	0.11	4	C
51	M	10.6	-8	0.11	4	C
52	F	18	-8	0.04	4	C
53	M	11	-3	0.03	4	C
54	M	13.3	-10	0.19	4	C
55	M	15.5		0.25	0	D
56	M	7.8	0	0.16	1	D
57	F	14	-3	0.24	4	C
58	F	17	-4	0.04	4	C
59	F	10.3		0.34	0	D
60	F	13.5	-1	0.17	4	C
61	M	12.4	-1	0.06	1	P
62	M	3.7	0	0.53	2	D
63	M	15.4	-12	0.28	4	C
64	M	12.8	-2	0.13	1	P
65	F	16	3	0.01	4	C
66	M	12.1	-10	0.07	4	C
67	M	4.1	-4	0.03	4	C
Summary for 2yr data	54% M	12.4	-5.1	N=6 (46%)		C=13

* Time points: 0, baseline; 1, 6 months; 2, 1 year; 3, 18 months; 4, 2 years
C, completed the 2 year study; D, dialysis; P, pre-emptive transplant

Summary for those completing the 2 year study
Means given for age and change in estimated GFR
Number and % of sample given for sex and protein: creatinine $\geq$ 0.1 g/ mmol (denotes substantial proteinuria)

Table 6.1.4 Baseline comparison of variables between those children that did and did not complete the 2 year period

Variable Mean & range	Mild		Moderate		Severe	
	Completed N= 19	Did not complete N=6	Completed N=19	Did not complete N=2	Completed N=13	Did not complete N=6
Age (yrs)	7.9 2.0-14.6	10.0 4.2-16.9	9.2 2.0-16.1	2.2 2.1-2.3	10.3 2.0-16.0	10.0 2.7-15.5
Primary disease (n=)	5 HUS, 7 RN, 4 OBS, 3 O	1 HUS, 4 RN, 1 OBS	9 RN, 5 OBS, 2 DYS, 1 O, 2 HUS	1 O, 1 DYS	2 DYS, 6 RN, 3 OBS, 1 HUS, 1 0	2 DYS, 1 RN, 1 HUS, 1 OBS, 1 O
Height SDS	-0.2 -2.1-2.1	-0.6 -2.6-0.7	-0.4 -2.4-1.5	-1.9 -2.5- -1.3	-1.5 -3.5- -0.2	-1.7 -3.7-1.1
BMI SDS	-0.1 -2.8-2.1	0.3 -1.4-2.3	0 -2.5-2.0	-1.0 -1.6- -0.4	-0.7 -2.4-0.7	0.2 -1.6-1.3
SBP SDS	1.1 -0.7-2.0	1.2 -0.7-2.0	1.3 0-2.0	Too young for SDS	1.0 -2.0-2.0	1.9 1.7-2.0
DBP SDS	0.8 -0.7-2.0	1.3 0.7-2.0	0.9 -0.7-2.0	Too young for SDS	0.9 -1.3-2.0	1.6 0.7-2.0
Protein: creatinine ratio	0.06 0-0.7	0 0	0.1 0-0.6	0.5 0-1.0	0.1 0-0.3	0.2 0.1-0.3

GFR, Glomerular filtration rate; HUS, Haemolytic Uraemic Syndrome; OBS, Obstructive nephropathy; RN, Reflux nephropathy; DYS, Hypo/dys plastic kidney; O, Other

Table 6.1.5 Prescription of medical & dietetic therapies at varying time points in children classified at baseline with mild CRI

Patient number	Nutritional suppl	Vitamin suppl	Anaemia Rx	Bone Rx	BP Rx	Sodium suppl
1			Iron: 2			
4			Iron: 0-4			
5						
6		OTC: 0-2	Iron: 3-4, DNT			
7		OTC: 0				
8		OTC if PI				
9					0-4: Ca-ch β-blocker ACEI	
10						
11						
12						
13						
14						
15						
16						
17						
18					ACEI: 1-4	
19		Kt: 0-3	Iron: 0-2			
20		Kt: 3-4				
21						
22			Iron: 0			
23					ACEI: 0-4	
24	Glucose P: 0-4	OTC: 0-1				
25						
26					ACEI: 3-4	
27						

Key:
Glucose P, Glucose polymer; CEF, complete enteral feed; MS, milk substitute;
OTC, Over the counter vitamin supplement; Kt, Ketovite tablet;
Iron, Oral iron supplement; EPO, erythropoietin;
1-Alpha, Alfacalcidol; CaCO3, Calcium carbonate;
Ca-ch, Calcium channel blocker; β-blocker, Beta-blocker; ACEI, ACE inhibitor;
NaCl, Sodium Chloride; NaHCO3, Sodium bicarbonate

Time points: 0, baseline; 1, 6 months; 2, 1 year; 3, 18 months; 4, 2 years
DNT, does not take regularly; PI, poor intake

Table 6.1.6 Prescription of medical & dietetic therapies at varying time points in children classified at baseline with moderate CRI

Patient number	Nutritional suppl	Vitamin suppl	Anaemia Rx	Bone Rx	BP Rx	Sodium suppl
28	Glucose P: 1-4	Kt: 1-4	Iron: 3-4	1-Alpha: 1-4		
29		Kt: 1-4		1-Alpha: 3-4		
30		Kt: 0-4	Iron: 1-2		ACEI: 4	
31						
32				1-Alpha: 4		
33						
34					ACEI: 0-4	
35				CaCO3: 2-4		
36			Iron: 1-2		ACEI: 2	
37	Glucose P: 0		Iron: 0-4	1-Alpha: 1-4		NaCl: 0
38		Kt: 0-4		1-Alpha: 0-4		
39		Kt: 0-4			0-2: Ca-Ch ACEI	
40				1-Alpha: 1-4		
41						
42				1-Alpha: 1-4, DNT		
43			Iron: 0-4, DNT	1-Alpha: 1-4, DNT	β-blocker: 0-4	
44	Glucose P: 0-4 DNT	Kt: 1-4	Iron: 1-4			
45		Kt: 0-4	Iron: 0-4	1-Alpha: 0-4		
46				1-Alpha: 0-4	ACEI: 0-4	
47		OTC: 0				
48						

Key:
Glucose P, Glucose polymer; CEF, complete enteral feed; MS, milk substitute;
OTC, Over the counter vitamin supplement; Kt, Ketovite tablet;
Iron, Oral iron supplement; EPO, erythropoietin;
1-Alpha, Alfacalcidol; CaCO3, Calcium carbonate;
Ca-ch, Calcium channel blocker; β-blocker, Beta-blocker; ACEI, ACE inhibitor;
NaCl, Sodium Chloride; NaHCO3, Sodium bicarbonate

Time points: 0, baseline; 1, 6 months; 2, 1 year; 3, 18 months; 4, 2 years
DNT, does not take regularly

Table 6.1.7 Prescription of medical & dietetic therapies at varying time points in children classified at baseline with severe CRI

Patient number	Nutritional suppl	Vitamin suppl	Anaemia Rx	Bone Rx	BP Rx	Sodium suppl
49	Glucose P: 0-4, DNT	Kt: 0-4	Iron: 0-4 EPO: 1-4	1-Alpha: 0-4		NaHCO3: 0-4
50	MS: 0-4	Kt: 0-2	Iron: 1-4	1-Alpha: 1-4		
51	Glucose P: 0-1	Kt: 0-4	Iron: 0-4	1-Alpha: 0-4 CaCO3: 0-4, DNT	ACEI: 0-4	
52	Glucose P: 2-3, DNT	Kt: 0-4	Iron: 1-4	1-Alpha: 0-4	ACEI: 0-4	
53				CaCO3: 0-4 1-Alpha: 1-4	ACEI: 0-4	
54			Iron: 1-4	1-Alpha: 0-4		
55			Iron: 0	0: 1-Alpha CaCO3	ACEI: 0	
56	Glucose P: 0-1	Kt: 0-1	Iron: 0-1	1-Alpha: 0-1		NaHCO3: 0-1
57	Glucose P: 0-4, DNT	Kt: 1-4	Iron: 0-4	1-Alpha: 0-4 Ca CO3: 2-4, DNT	0-4: Ca-ch β-blocker	
58		Kt: 0-4	Iron: 0-4	1-Alpha: 0-4		
59	MS: 0			1-Alpha: 0		
60				CaCO3: 0-4 1-Alpha: 1-4	0-4:Ca-ch β-blocker ACEI	
61	Glucose P: 0-1	Kt: 0-1		1-Alpha: 0-1		NaHCO3: 0-1
62	CEF: 0-2 MS: 0-1	Kt: 0-2		1-Alpha: 0-2 CaCO3: 0-2		NaHCO3: 0-2
63		Kt: 0-4	Iron: 1-4	1-Alpha: 0-4 CaCO3: 3-4	ACEI: 0-3 β-blocker: 4	NaHCO3: 0-4
64			Iron: 0-1 EPO: 0-1	1-Alpha: 0-1 CaCO3: 0-1	Ca-ch: 1	
65		Kt: 4	Iron: 2-4		Ca-ch & ACEI: 0-4; β-blocker: 0-2	
66	Glucose P: 2-4	Kt: 1-4		1-Alpha: 0-4 CaCO3: 4	ACEI: 0-4	
67	Glucose P: 0-4		Iron: 0-4	1-Alpha: 0-4		NaHCO3: 0-4

Glucose P, Glucose polymer; CEF, complete enteral feed; MS, milk substitute;
OTC, Over the counter vitamin supplement; Kt, Ketovite tablet;
Iron, Oral iron supplement; EPO, erythropoietin;
1-Alpha, Alfacalcidol; CaCO3, Calcium carbonate;
Ca-ch, Calcium channel blocker; β-blocker, Beta-blocker; ACEI, ACE inhibitor;
NaCl, Sodium Chloride; NaHCO3, Sodium bicarbonate

Time points @: 0, baseline; 1, 6 months; 2, 1 year; 3, 18 months; 4, 2 years
DNT, does not take regularly

Table 6.1.8 Change in prescription of medical and dietetic therapies over the two year period between the groups of children with CRI

Dietetic/ medical therapy	Mild Number (%) receiving therapies Baseline N= 25	1 yr 21	2 yr 19	Moderate Number (%) receiving therapies Baseline N= 21	1 yr 20	2 yr 19	Severe Number (%) receiving therapies Baseline N= 19	1 yr 14	2 yr 13
Glucose polymer	1 (4)	1 (5)	1 (5)	2 (10)	2 (10)	2 (11)	6 (32)	5 (36)	4 (31)
Complete enteral feed							1 (5)	1 (7)	
Milk substitute							3 (14)	1 (7)	1 (8)
Vitamin Supplements: OTC preparation	4 (16)	2 (10)	1 (5)	1 (5)					
Ketovite tablet	1 (4)	1 (5)	1 (5)	4 (19)	7 (35)	7 (37)	9 (47)	9 (64)	8 (62)
Iron	3 (12)	3 (12)	2 (11)	3 (14)	6 (30)	5 (26)	8 (42)	10 (71)	10 (77)
Erythropoietin							1 (5)	1 (7)	1 (8)
Alfacalcidol				3 (14)	8 (40)	10 (53)	15 (79)	13 (93)	12 (92)
Calcium carbonate					1 (5)	1 (5)	6 (32)	5 (36)	6 (46)
Ca-channel blocker	1 (4)			1 (5)			3 (16)	3 (21)	3 (23)
Beta blocker	1 (4)			1 (5)	1 (5)	1 (5)	3 (16)	3 (21)	3 (23)
ACE inhibitor	2 (8)	3 (16)	4 (21)	3 (14)	4 (20)	3 (16)	8 (42)	7 (50)	6 (46)
Sodium bicarbonate							6 (32)	4 (29)	3 (23)

6.2 Growth, other anthropometric indices, energy and protein intakes

6.2.1 Anthropometry

Individual height, weight and BMI SDS's over the 2 year period and the changes in these parameters in those who completed 1 and 2 years of the study are depicted for each group of CRI in Figures 6.2.1.1 - 6.2.1.3 and Tables 6.2.1.1 – 6.2.1.3 respectively (appendix 3). Twelve (63%) children with mild CRI completing the 2 year study showed an improved height SDS, as was the case for 9 (47%) of children with moderate CRI and 9 (69%) of children with severe CRI. The most remarkable change was the dramatic improvement observed in height SDS in one child with mild CRI (24), who was one of the youngest in the study, was only known to a dietitian for 6 months and who was the only child with mild CRI to be take a glucose polymer for the duration of the study. This child also exhibited a substantial increase in weight SDS during the study, such that his BMI SDS did not greatly change. Nine (47%) children with mild CRI who completed the 2 year study showed an increase in BMI SDS, whereas 13 (68%) with moderate CRI, and only 3 (23%) with severe CRI, exhibited an increase in BMI SDS.

Some of the most notable changes included the substantial increase in BMI SDS in a prepubertal child (28) with moderate renal failure during the first 6 months of the study, which coincided with prescription of a glucose polymer following baseline consultation. Also in the moderate group, a substantial reduction in BMI SDS was noted in one child (36) at 1 year who subsequently required dialysis, and despite prescription of a glucose polymer, one child (44) continued to exhibit poor weight gain due to poor compliance to supplements and a poor appetite. One subject with moderate CRI (37) had a fluctuating appetite depending upon whether he was suffering from a urine infection or not, and over the 2 year period he was able to catch-up weight lost, without the ongoing use of a glucose polymer. Children 32, 42 and 43 were of pubertal age, and appeared to lose height SDS during the study, which is likely to be associated with delayed pubertal growth spurts. In the severe group, the child (67) who showed the greatest improvement in weight and BMI SDS was one of the youngest children in the study, who had been known to the dietitian since birth and responded well, following baseline assessment, to an increase in the amount of energy-based supplements prescribed. The greatest loss in weight and BMI SDS in this group occurred in a child (65), whose renal

function remained stable, and whose weight loss was due to development of anorexia nervosa.

Comparisons of mean changes in height, weight, BMI and MUAC between the groups in those who completed the 2 year period compared to baseline are depicted in Table 6.2.1.4. For all anthropometric parameters, a smaller increase over the two years was observed in those with severe CRI compared to the other two groups. Lower SDS scores for all indices did not support this however, as height SDS improved over the 2 year period. Height SDS also improved in those with mild but not moderate CRI. Ten children at baseline had height SDS scores below –2 SDS (2 with mild CRI, 3 moderate CRI, 5 severe CRI). Of these children, the one child (9) with mild CRI who completed the study exhibited a height SDS that crossed the cut-off of –2 SDS, probably as a result of a delayed pubertal growth spurt. Two of the three children with moderate CRI completed the study (38, 44), but although an increase in height SDS was observed, neither of them improved their height sufficiently to cross the –2 SDS cut-off. Neither of the children was of an age where catch-up pubertal growth was expected. Child 39 however, gained height SDS that was likely to be associated with pubertal catch-up growth. Three of the five children with severe CRI, with baseline height SDS's < -2 SDS completed two years (49, 60, 66), of which only one child (60) crossed the -2 SDS cut-off and this child exhibited catch-up growth following a delayed pubertal growth spurt. Children 57 and 58 also gained height SDS that was likely to have been a result of catch-up pubertal growth. Weight SDS decreased in those with severe CRI, whereas an increase in weight SDS was observed in the other groups. Changes in BMI SDS were reflected by similar but smaller changes in MUAC SDS. Only those with moderate CRI exhibited an increase in these indices over time.

In addition to observing the absolute change in anthropometric measurements between baseline and the end of the 2 year period as described above, a general linear model such as a UNIANOVA can be used to statistically compare changes in anthropometry during the 2 year period. UNIANOVA involves calculating the best fit between the observed changes in each variable over time, for each individual or the group as a whole, in comparison to baseline. This also enables all children participating in the longitudinal study to be included in the analysis and not purely those who completed the full 2 year period. Significant changes were observed in height SDS over time for the

group as a whole using UNIANOVA, and these changes were significantly different between the groups, with an improvement in height SDS being noted in those with mild CRI and a greater improvement in those with severe CRI (Table 6.2.1.4). The improvement in height SDS for those with mild CRI however, was not noted if the extreme outlier (24) was excluded, and neither was there any significant change over time noted in those with moderate CRI. Change in weight SDS over time was not significant for the group as a whole, or between the differing levels of severity of CRI. The change in BMI SDS was also not significant for the cohort as a whole, but there were differences between groups, with those with severe CRI exhibiting a significant reduction in BMI over time. There were however, no differences observed in MUAC SDS over time.

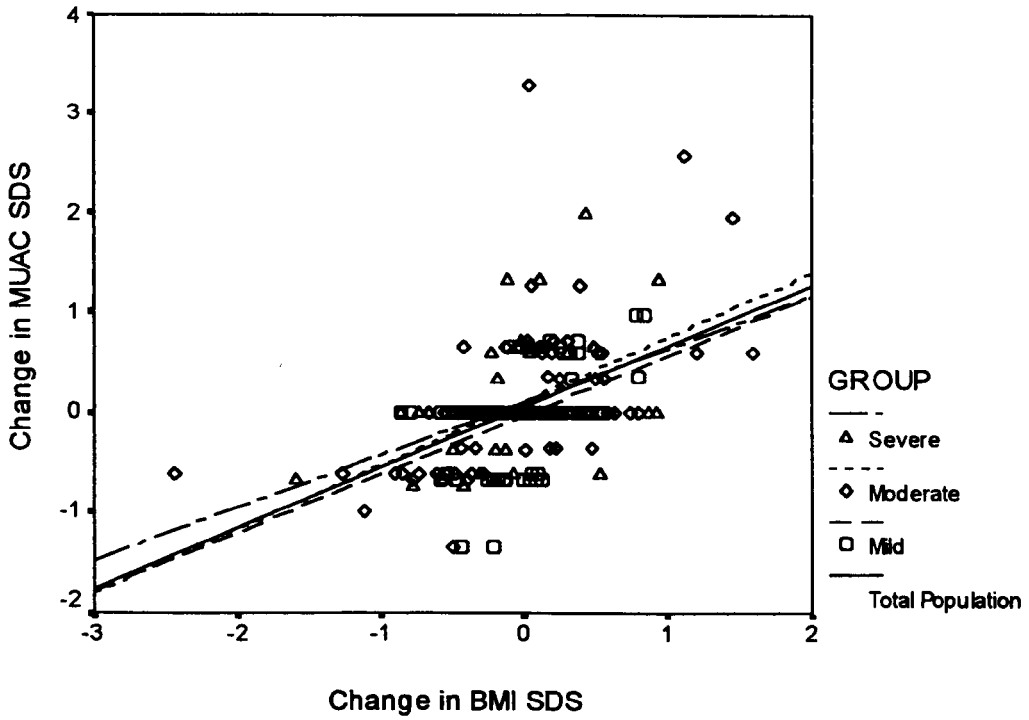
Simple linear regression was conducted to determine whether there was a correlation between the changes in MUAC SDS and BMI SDS over the 2 year period (Figure 6.2.1.4). A significant correlation was found (R^2=0.24). There was also a significant correlation between the changes in MUAC SDS and weight over the 2 year period, although the correlation was weaker (R^2=0.16).

Table 6.2.1.4 Comparison of mean change in height, weight, BMI and MUAC in those who completed the 2 year study in relation to severity of CRI

Growth Parameter Mean change (SD)	All (n=51)	Mild CRI (n=19)	Moderate CRI (n=19)	Severe CRI (n=13)
Height				
cm	11.27 (4.54)	12.95 (4.50)	10.70 (4.01)	9.65 (4.85)
SDS	0.07 (0.41)	0.18 (0.50)	-0.07 (0.36)	0.10 (0.32)
Significance	[F=6.97; 1df, p=0.009]	[F=4.91; 1df, p=0.03] +	[F=1.37; 1df, p=0.245]	[F=9.45; 1df, p=0.003]
Weight				
kg	6.63 (4.45)	7.05 (4.08)	7.94 (4.59)	4.08 (4.00)
SDS	0.01 (0.48)	0.07 (0.39)	0.07 (0.45)	-0.18 (0.61)
Significance	[F=0.26; 1df, p=0.612]	[F=1.86; 1df, p=0.176]	[F=0.836; 1df, p=0.363]	[F=2.18; 1df, p=0.145]
BMI				
kg/m^2	0.69 (1.39)	0.54 (1.29)	1.24 (1.51)	0.11 (1.11)
SDS	-0.05 (0.52)	-0.11 (0.41)	0.16 (0.48)	-0.27 (0.64)
Significance	[F=0.96; 1df, p=0.329]	[F=1.92; 1df, p=0.170]	[F=1.69; 1df, p=0.198]	[F=8.33; 1df, p=0.006]
MUAC				
cm	1.41 (1.39)	1.46 (1.39)	1.74 (1.41)	0.79 (1.24)
SDS	0.02 (0.56)	-0.05 (0.51)	0.12 (0.51)	-0.05 (0.72)
Significance	[F=0.08; 1df, p=0.779]	[F=0.08; 1df, p=0.782]	[F=0.06; 1df, p=0.810]	[F=0.33; 1df, p=0.570]

SDS, standard deviation score; BMI, body mass index; MUAC, mid upper arm circumference
Significance is determined by UNIANOVA for changes over time, observations made at 6 monthly intervals for 2 yrs
+ Exclusion of outlier [F=1.53; 1df, p=0.220]

Figure 6.2.1.4 Correlation between change in MUAC SDS and BMI SDS over the 2 year period



Correlation between change in body mass index (BMI) & mid upper arm circumference (MUAC) standard deviation scores (SDS):

$y= 0.607x + 0.08$ [R^2=0.24; F=33.41; 2,208df, p<0.0001]

Correlation between change in weight & MUAC SDS (not shown in figure):

$y= 0.588x + 0.08$ [R^2=0.16; F=19.90; 2,208df, p<0.0001]

6.2.2 Energy and protein intakes

Individual energy and protein intakes over the 2 year period and the changes in these parameters in those who completed 1 and 2 years of the study are depicted for each group of CRI in Figures 6.2.2.1 – 6.2.2.2 and Tables 6.2.2.1 - 6.2.2.3 respectively (appendix 3). Two children with mild CRI (4, 13) consistently reported increased energy intakes compared to baseline, which was accompanied by a small increase in BMI SDS. They were both male children of an identical age (7 years by the end of the study) who had reported lower than average energy intakes at baseline (Table 5.2.1, appendix 2) and who were able to improve their energy intake, following encouragement to do so, due to below average BMI's (Table 5.1.1, appendix 2). There were 6 children who reported consistently lower energy intakes compared with baseline. Two of these children (14, 27), who were 6 and 9 years old respectively, reported substantial reductions in energy intake, equivalent to $\geq$ 25% EAR by the end of the study period. The child (27) with reflux nephropathy had been advised to reduce his energy intake in association with a high BMI and raised BP, whilst the other, who had had HUS, was advised to replace the large intake of high-energy snacks resulting in a high total energy intake, with more fruit and a generally healthier diet. Despite this, child 27 continued to exhibit an increase in weight and BMI SDS, whilst child 14 demonstrated a reduction in these parameters. Two children (10, 17) also had high BMI's at the outset, with child 10 also exhibiting raised BP, and in line with dietetic advice, reported reductions in energy intake of 20% EAR by the end of the first year. This was only accompanied by a reduction in BMI SDS in child 17, at 1 year, but not at 2 years. Unfortunately, one child (10) was transferred to the adult renal unit at 1 year and the other failed to provide a 2 year food diary for analysis. Child 23 was an adolescent girl who was keen to watch her weight, despite having a BMI below average, and reduced her energy intake, irrespective of the dietary advice given.

The youngest child of the group (24), with a low BMI at baseline, was the only one to be prescribed a glucose polymer, which increased the reported energy intake to substantially above the average and was accompanied by an increase in growth. The quantity of supplement taken (as %EAR) halved over the 2 year period, which resulted in a slight reduction (1% EAR) in energy intake by the end of the study. Child 13 was the only one with mild CRI to report an energy intake < 80% EAR at baseline. Subsequent reported energy intakes were not suboptimal, due to a substantial increase in

energy intake, associated with recommendations to increase fats, sugars and snacks. Child 19, a girl of pubertal age, had a markedly low BMI at baseline, despite an apparent average energy intake and as a result was encouraged to increase her intake of fats, sugars and snacks. Although the advice appeared to be reasonably unsuccessful, with a substantial reduction in reported energy intake by the end of the study, she demonstrated an increase in weight and BMI SDS, which may be indicative of under-reporting the changes adopted (Table 6.2.2.4).

In those with moderate CRI, of marked interest was the substantial increase in energy intake reported by child 28, who was prescribed an energy supplement following baseline assessment, which revealed a very poor energy intake and low BMI. Compliance to the supplement was achieved throughout the study and a significant increase in weight gain ensued. Height SDS started to improve during the second year in this child. Conversely, a substantial reduction in total energy intake occurred in the 2 year old (37), whose appetite improved during the study, following surgery to prevent further urinary reflux, and as a consequence, a reduction in the number of urinary tract infections, which resulted in a poor appetite, occurred. The resulting total energy intake however, was appropriate for age without the use of a nutritional supplement, and weight SDS was maintained by the end of the study. Child 44 appeared to be heavily dependent on nutritional supplements to achieve an adequate energy intake, and despite this, her energy intake remained suboptimal, although it seemed to have improved over the study period. A substantial reduction in energy intake occurred in child 36, which was associated with weight loss and the need for dialysis, one year into the study.

The oldest girl in the study (30), who failed to complete a diary at 1 year, revealed a reduced energy intake compared with baseline at 2 years. Despite this, she continued to gain weight SDS, suggestive of under-reporting and height SDS also increased, possibly indicating continuation of a delayed growth spurt. Three male children of 9-10 years of age at baseline (40, 41, 47) appeared to make substantial reductions to their energy intake over the 2 year period, following advice to control their weight gain and blood pressure. In two children (40, 41), this was associated with an increase in weight and BMI SDS, which is therefore more suggestive of under-reporting than concordance with treatment (Table 6.2.2.4). Child 29, who was younger (5 years at baseline) and only reported an energy intake of 81% EAR at baseline, reported increased energy intake by

using more fats and sugars as advised, resulting in an increase in weight and height SDS. The mother of this child notably strictly adhered to the advice given throughout the study. The mother of child 46, an adolescent girl however, had ongoing concerns about the poor dietary intake of her child, which was supported by the suboptimal energy intake at baseline. The girl was able to increase her energy during the study, but the overall energy intake was still be considered to be suboptimal (75% EAR). Despite this, she was able to increase her BMI SDS over the 2 years.

In the severe group, five children (50, 53, 62, 63 and 65) reported substantially lower energy intakes ($\geq$ 20% reduction in EAR) during the study period. The youngest child in the group (62) entered the dialysis programme at one year. Two children were 13 years of age (63, 65) at baseline, with acceptable BMI SDS and average energy intakes. Over the 2 year period they both exhibited a reduction in their BMI SDS, with height SDS also being lower compared with baseline. A reduction in energy intake was associated with development of anorexia nervosa in one child (65) and deteriorating appetite associated with worsening renal failure in the other (63). Child (50) was young (4 years age at baseline), small in stature and underweight (Table 5.1.3, appendix 2), and despite an apparent reduction in energy intake, exhibited an increase in weight and height SDS over the 2 year period (Table 6.2.1.3, appendix 3). This would suggest that energy intake was under-reported in this child, although the initial reported energy intake was exceptionally high (146% EAR), and it is more likely that the baseline energy intake was over-reported. The latter was also likely to apply to child 53, who reported a substantial reduction in energy intake by the end of the study, which was not accompanied by a reduction in BMI SDS.

The oldest child in the group (52) had a low BMI SDS and supplements were commenced which appeared to increase energy intake temporarily, although this was not accompanied by weight gain, and it became clear that these supplements were not taken regularly, and were subsequently stopped. An increase in height SDS was observed, which was likely to be associated with a delayed pubertal growth spurt. The only child (62) to receive a complete nutritional supplement via a gastrostomy button obtained 75% of his total energy intake by this route, resulting in an energy intake above average for age. Despite an improvement in BMI SDS prior to the study, he did not exhibit any catch-up growth, and required dialysis one year into the study. During

his only year in the study, a reduction in energy intake from foods occurred, which may have been associated with worsening anorexia associated with his deteriorating condition, and there were also concerns that he was not receiving the overnight feed as regularly as prescribed. Children 54, 60 and 67 reported consistent improvement in their energy intake compared with baseline. Child 67 was the youngest in the group, and as he got older, was able to improve his total energy intake, by increasing energy intake from solids and reducing the amount of energy derived from the nutritional supplement. This was accompanied by an improvement in growth and weight gain (Table 6.2.1.3, appendix 3). The other 2 children were both 11 years of age at baseline (1 male, 1 female), both of an acceptable BMI, but shorter than average. They both exhibited catch-up in height, with an increase in height SDS that was greater than the increase in weight SDS. Their reported energy intakes at baseline were relatively low (80% EAR, Table 5.2.3, appendix 2) and it is likely that some of the reported increase in energy intake was due to under-reporting at baseline (Table 6.2.2.4). One child (57) was unable to maintain as great an energy intake from supplements as at baseline, resulting in a reduced total energy intake, which was accompanied by a reduction in weight and BMI SDS. Height SDS increased however in this child, which may be associated with some catch-up pubertal growth. Despite the reduction in energy, total energy intake remained above 80% EAR by the end of the study. Child 49 began the study with a third of her energy intake being derived from an energy supplement, and nevertheless only reported an energy intake of 78% EAR. During the study, she reported a slightly increased energy intake, taking it above the 80% EAR minimum target, despite a substantial reduction in the amount of energy derived from the supplement. This had not been advised, but was associated with difficulties in continuing to take the supplement. The suboptimal energy intakes at baseline in children 55 and 56 were related to anorexia associated with the need for dialysis, which they both received during the first year of the study.

Attempts were made to validate the reported energy intakes against recently proposed cut-offs for children (Torun et al, 1996) for the ratio EI: BMR, BMR being estimated from Schofield equations (1985). Table 6.2.2.4 illustrates the mean cut-off for children of different ages and sex between the groups of CRI, and the number of children that fall within the minimum and maximum proposed values. The number of children within the age bands changed, as the children moved between bands or left the study

during the 2-year period. In children under 6 years of age, the three with severe CRI at baseline showed a substantial reduction in EI: BMR during the two year period, which was not so apparent in the other two groups of CRI. This age group was consistently associated with a number of children with an EI: BMR ratio above the upper cut-off limit, thereby being classified as over-reporters. Energy intake was reported to be much greater than average in 3 children with severe CRI (2 < 6 years age), two of whom were in receipt of nutritional supplements, and 1 young child with moderate CRI, who was also in receipt of an energy supplement. In the older children (6-18 years of age) however, the mild group exhibited the greatest change in reporting pattern over the two year period, with all boys appearing to report acceptable energy intakes at baseline, whereas at 12 and 24 months, half of them became classified as under-reporters of energy intake. A similar pattern was observed in the girls of this age group with mild CRI. At least four of these children however, had been advised to reduce their energy intake, associated with raised BMI and BP. In those with moderate CRI, although consistent over time, a number of girls and boys were considered to be under-reporters of energy intake, according to the EI:BMR ratio. It was felt that under-reporting had occurred, as an increase in weight and BMI SDS had been observed in at least 2 boys and 1 girl with a low EI:BMR ratio. In contrast, in those with severe CRI, both girls and boys appeared to consistently report acceptable energy intakes. One girl with a low EI:BMR ratio developed anorexia nervosa, and the reported energy intake was therefore likely to have been a true representation of actual intake.

The median and interquartile range for changes in energy and protein intakes after one and two years within each group are described in Table 6.2.2.5. There was a reduction in median energy intake as a %EAR over the 2-year period for the cohort as a whole, with the reduction being more pronounced during the second year of the study. Those with mild CRI exhibited the greatest reduction in energy intake (10% decrease in energy as a % EAR). The reduction in energy intake over time (inclusive of energy supplements), as analysed by UNIANOVA, was significant for the cohort as a whole (P=0.036), but the decrease for those with mild CRI did not reach significance (p=0.067). Only one child with mild CRI was in receipt of nutritional supplements during the whole 2-year period, providing less than 100 kcal/ day (Table 6.1.5). In those with moderate CRI, two children at baseline and two thereafter took energy supplements over the study period, the median energy intake remaining similar for the

duration at approximately 450 kcal/ day (Tables 6.1.6 & 6.1.8). Children with severe CRI showed a median increase in energy intake as a % EAR from foods alone, whilst their median total energy intake including energy from supplements, decreased during the second year (Table 6.2.2.5). At one year, similar to baseline, 43% of children with severe CRI were in receipt of nutritional supplements providing a median of 300 kcal/ day (milk substitutes are not counted as a nutritional supplement). This reduced to 31% of children at the end of the 2-year period, providing a median of 200 kcal/ day (Tables 6.1.7 & 6.1.8). The reduction in total energy intake in those with severe CRI was not deemed to be significant by UNIANOVA (Table 6.2.2.5).

Eight children with mild CRI were able to reduce their protein intake over the whole 2-year period, compared with baseline protein intakes (Table 6.2.2.1, appendix 3). Of these children, three (19, 20, 21) successfully achieved the recommended intake for protein of 0.8-1.2 g/kg/d. Five children exhibited an increase in protein intake in the first year, followed by a reduction in the second year. Only one child (1) did not report a reduction in protein intake during the whole 2-year period. One child (27) reported a substantial reduction in protein intake, which was associated with a large reduction in energy intake and was a result of attempts to reduce total energy and protein intake. Only 2 children (10, 23) had protein intakes that met the recommended intake at baseline, and who were able to maintain their intakes close to these recommendations throughout the study. In both cases, a reduction in energy intake was noted during the study, which had only been advised in child 10.

In those with moderate CRI, 9 children were reported to have reduced their protein intake over the whole 2 year period (Table 6.2.2.2, appendix 3), whilst 3 exhibited an increase in year one, followed by an overall reduction in protein intake by the end of the study. Of all these children, only two (40, 41) reported protein intakes that met with the recommendations by the end of the study, and there was concern that these two children under-reported their actual intakes. Four children (39, 42, 44 and 46) commenced the study with protein intakes close to that recommended, ranging from 0.9-1.2 g/kg. Of these children, one was able to reduce their intake a little further (39), two increased their intake slightly to take them above that recommended (42, 44) and child 46, despite an increase, continued to have an acceptably low protein intake. Three children reported an increase in protein intake during the study, which was particularly notable in

child 37. This was related to a poor dietary intake at baseline, where energy intake was supplemented with a glucose polymer, and which was subsequently associated with an improved appetite and greater intake of nutrition from solid foods. Four children (28, 29, 35 and 38) demonstrated an increase in energy intake with a decrease in protein intake.

For children with severe CRI, despite the lower median protein intake at baseline, five children were able to reduce their protein intake over the whole 2-year period, although 4 children did report an increase in protein intake over this time (Table 6.2.2.3, appendix 3). The pattern of an increase in protein intake in the first year followed by a reduction in the second year was not apparent in this group. Only one (63) of the five children, who were able to reduce their protein intake by the end of the study, achieved a protein intake in line with that recommended, but unfortunately this was associated with anorexia due to deteriorating renal function. The two greatest reported reductions in protein intake (50, 53; children of 4 and 8 years of age respectively) were also observed for energy intake, which is likely to be due to over-reporting at baseline. Two children (54, 67) reported reduced protein intakes whilst reporting an increase in energy intake. One of the oldest children (65) had a very low protein intake at baseline (0.6g/kg), whilst achieving an adequate energy intake without the use of supplements. Reported protein intake reduced by one year, associated with a reduction in energy intake, but this was in the girl who was developing anorexia nervosa. Children 55, 57 and 59 had protein intakes at baseline in line with recommendations. Unfortunately, two of these children (55, 59) who had been receiving ongoing dietetic support for at least 2 years prior to the study, required dialysis soon after recruitment to the study. The other adolescent child was able to maintain her protein intake throughout the study period.

Actual protein intake (g/ kg) fell each year over the 2 year period in all groups, with a median reduction of approximately 0.4.g/kg/d from baseline to the 2 year end point (Table 6.2.2.5). This was deemed to be significant over time by UNIANOVA, for the cohort as a whole ($p<0.0001$) and for those with mild ($p=0.007$) and moderate CRI ($p=0.011$). When described as a % of total energy intake, despite a reduction in energy intake, those with mild CRI showed a median reduction in % total energy from protein. This was also the case for those with moderate CRI by the end of the 2-year period,

whereas those with severe CRI exhibited an increase in median protein intake as a % of total energy intake.

Linear regression was used to determine whether there was any correlation between change in weight or height SDS with change in energy intake over the 2-year period (Figure 6.2.2.3). Significant correlations existed for the cohort as a whole for both height and weight SDS. For weight, this observation was greatest in those with moderate CRI, with 23% of the variation in weight SDS being attributed to a change in energy intake. Change in height SDS was highly correlated to change in energy intake in those with severe CRI, with the equation; $y= 0.01x - 0.07$, with 50% of the variation in height SDS being explained by a change in energy intake. The relationship between change in height SDS and change in energy intake weakened with reduction in severity of renal disease. Correlation between actual energy intake and change in height SDS over the two-year period was not significant however, for the whole cohort, or any of the groups individually, although those with severe CRI had an R^2 value of 10%. Correlations between change in height SDS and change in the individual macronutrients was not significant.

Table 6.2.2.4 Validation of reported mean energy intakes using EI:BMR cut-offs over the two year period between groups

	Mild			Moderate			Severe		
Time (mths)	0	12	24	0	12	24	0	12	24
0-5 yrs age									
EI:BMR [mean (SD)]	1.83 (0.42)	1.78 (0.24)	1.77 (0.34)	1.91 (0.43)	1.72 (0.18)	1.87 (0.05)	2.57 (0.72)	1.91 (0.36)	1.76
No. within/out cut-off*	5/8 (3 >)	2/5 (3 >)	2/4 (2>)	4/7 (3 >)	2/3 (1 >)	0/2 (2 >)	1/3 (2 >)	1/3 (2 >)	1/1
6-18 yrs age (boys)									
EI:BMR [mean (SD)]	1.63 (0.22)	1.49 (0.36)	1.48 (0.35)	1.51 (0.26)	1.55 (0.36)	1.46 (0.36)	1.70 (0.48)	1.94 (0.42)	1.83 (0.40)
No. within/out cut-off*	8/8	7/10 (3 <)	6/10 (4 <)	4/8 (4 <)	10/13 (3 <)	7/11 (4 <)	5/7 (1 <, 1>)	3/5 (2 >)	4/5 (1 >)
6-18 yrs age (girls)									
EI:BMR [mean (SD)]	1.55 (0.30)	1.39 (0.38)	1.50 (0.47)	1.38 (0.43)	1.33 (0.34)	1.37 (0.22)	1.52 (0.17)	1.54 (0.23)	1.50 (0.16)
No. within/out cut-off*	5/7 (2 <)	3/5 (2 <)	1/3 (2 <)	2/3 (1 <)	2/3 (1 <)	2/3 (1 <)	8/8	5/6 (1 <)	4/4

EI, Energy intake; BMR, Estimated basal metabolic rate (Schofield, 1985)
*Cut-off range (Torun et al, 1996): 0-5 yrs age: 1.28-1.79; 6-18 yrs age, boys 1.39-2.24; girls 1.3-2.1
The fraction denotes the number of children within the cut-off range;
< denotes the number of children with an EI:BMR below the lower limit cut-off;
> denotes the number with an EI:BMR above the upper limit cut-off

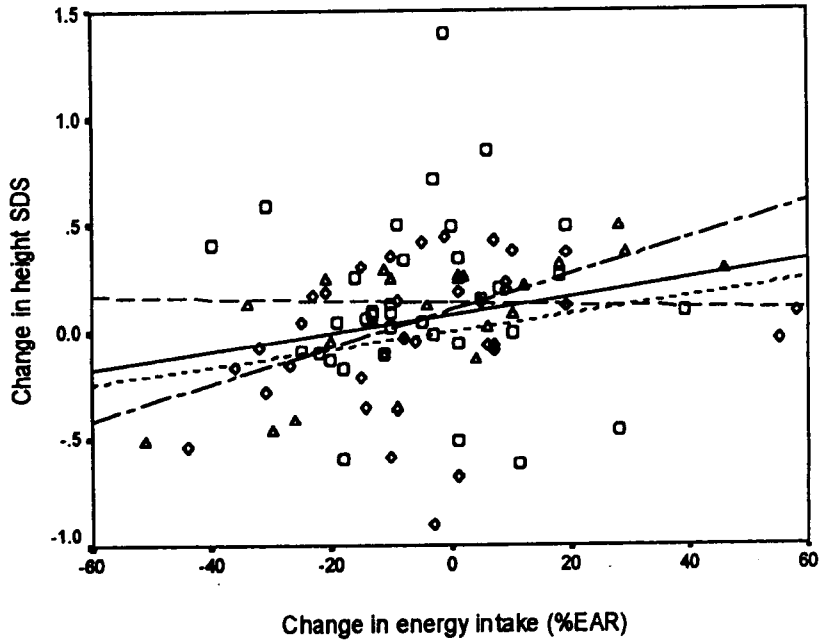
Table 6.2.2.5 Comparison of changes from baseline in energy and protein intakes in those who completed 1 & 2 years of the study in relation to severity of CRI

Change in nutrient Median (interquartile range)		All (N= 50; 42)*	Mild (N= 19; 16)*	Moderate (N= 18; 16)*	Severe (N= 13; 10)*
Energy (- suppl) (% EAR)	Year 1	-1 (-10.3 – 7)	-3 (-14 – 7)	-2.5 (-11 – 7)	2 (-10 – 10.5)
	Year 2	-6.5 (-15.8 – 10.5)	-10 (-18 – 4.5)	-2 (-15 – 6.5)	7.5 (-14 – 22)
Significance		[F=2.3; 1df, p=0.135]	[F=3.3; 1df, p=0.077]	[F=0.7; 1df, p=0.420]	[F=0.1; 1df, p=0.817]
Energy (+ suppl) (% EAR)	Year 1	-3 (-14 – 6.3)	-3 (-14 – 6)	-4.5 (-16.8 – 7)	1 (-19.5 – 8)
	Year 2	-8.5 (-18.5 – 7.5)	-10 (-18 – 3.5)	-6.5 (-19.5 – 8.5)	-7 (-20 – 16)
Significance		[F=4.6; 1df, p=0.036]	[F=3.6; 1df, p=0.067]	[F=0.6; 1df, p=0.430]	[F=0.6; 1df, p=0.446]
Protein [as % energy (+ suppl)]	Year 1	0.6 (-1.9 – 2.4)	-0.3 (-2 – 1)	0.8 (-1.1 – 2.9)	0.8 (-2.1 – 3.9)
	Year 2	-0.4 (-1.7 – 1.2)	-0.4 (-1.6 – 1.1)	-0.9 (-1.8 – 0.3)	1.4 (-2.5 – 2.2)
Significance		[F=0.2; 1df, p=0.697]	[F=0.0; 1df, p=0.837]	[F=0.6; 1df, p=0.428]	[F=0.1; 1df, p=0.738]
Protein [as % energy (- suppl)]	Year 1	0.3 (-2.2 – 2.5)	-0.3 (-2.3 – 1)	0.8 (-1.1 – 2.8)	0.8 (-3.4 – 4.2)
	Year 2	-0.4 (-1.8 – 0.7)	-0.4 (-1.7 – 0.6)	-0.7 (-1.8 – 0.3)	0.6 (-3.1 – 1.8)
Significance		[F=1.2; 1df, p=0.271]	[F=0.5; 1df, p=0.493]	[F=0.8; 1df, p=0.391]	[F=0.2; 1df, p=0.667]
Protein (g/kg)	Year 1	-0.2 (-0.5 – 0.3)	-0.2 (-0.6 – 0.2)	-0.2 (-0.5 – 0.4)	0 (-0.5 – 0.4)
	Year 2	-0.4 (-0.6 – 0)	-0.4 (-0.6 - -0.1)	-0.4 (-0.7 – 0.2)	-0.3 (-0.7 – 0.2)
Significance		[F=16; 1df, p<0.0001]	[F=8.3; 1df, p=0.007]	[F=7.3; 1df, p=0.011]	[F=2.8; 1df, p=0.107]

*N= (Year 1; Year 2); EAR, expected average requirement; suppl, nutritional supplement;
Significance is determined by UNIANOVA for changes over time, observations made at 6 monthly intervals for 2 yrs

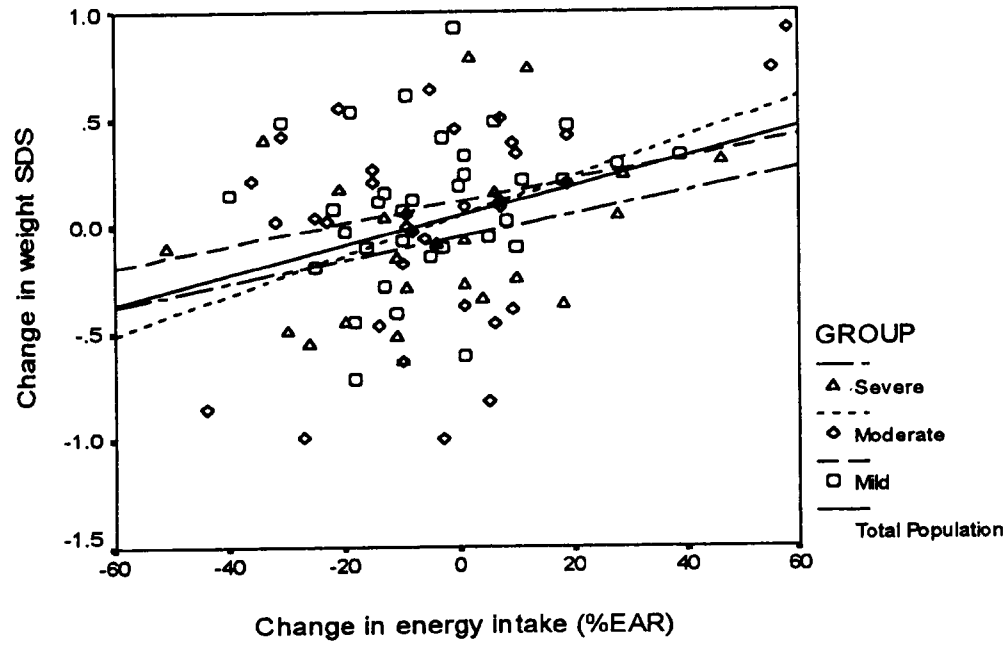
Figure 6.2.2.3 Correlation between changes in energy intake and change in a) height SDS and b) weight SDS between groups

a)



Total [R^2=0.07; F=3.21; 2,89df, P=0.045]
Mild CRI [R^2=0.01; F=0.18; 2,32df, P=0.835]
Moderate CRI [R^2=0.08; F=1.26; 2,31df, P=0.298]
Severe CRI [R^2=0.50; F=10.05; 2,20df, P=0.001]

b)



Total [R^2=0.12; F=6.12; 2,89df, P=0.003]
Mild CRI [R^2=0.06; F=0.98; 2,32df, P=0.388]
Moderate CRI [R^2=0.23; F=4.73; 2,31df, P=0.016]
Severe CRI [R^2=0.10; F=1.07; 2,20df, P=0.362]

6.3 Macronutrient intake and hyperlipidaemia

Changes in individual fat and carbohydrate intakes in those who completed 1 and 2 years of the study are depicted for each group of CRI, in Tables 6.3.1 – 6.3.3 (appendix 3). In all but one child (40), the children who had been advised to reduce their total energy intake reported lower total fat intakes, compared with baseline. In the majority of cases, this involved a reduction in saturated fat intake. Energy intake from sugars was also reduced in the majority of these children. Of the 3 children with mild CRI who increased their energy intakes as advised, two children (4, 24) predominantly achieved this by increasing total fat intake, with little change in saturated fat intake, whilst child 13 increased his energy intake predominantly via an increase in sugars (Table 6.3.1, appendix 3). This resulted in child 13 being the only one to have a total sugar intake that exceeded 30% of total energy intake by the end of the study, compared to 4 children, of which child 13 was not one, at baseline (Table 5.2.6, appendix 2). Five children at the end of the study compared to 2 (7, 19) at baseline, reported saturated fat intakes that fell within recommendations for the healthy population of < 11% total energy.

In those with moderate CRI, the substantial increase in energy intake from the prescription of an energy supplement in child 28 was represented by a large increase in total carbohydrate rather than sugars, the supplement being a glucose polymer rather than simple sugars. In child 37, whose appetite improved and supplements were stopped, energy derived from carbohydrates fell, but was replaced by a substantial increase in energy from total fat, which involved an increase in all fatty acids. Child 44 demonstrated an improvement in energy intake during the study, associated with an increase in total fat and saturated fat compared with carbohydrate, which fell during the study. The increase in energy intake that was reported in child 29 was associated with a substantial increase in total carbohydrate, predominantly associated with an increase in sugars, bringing total sugar intake to well above 30% of total energy, and this was accompanied by a substantial reduction in total energy from fat. One other child (48) with moderate CRI had a very high sugar intake at the end of the study, compared with a total of 5 children who exceeded 30% of energy at baseline. Six children at the end of the study had saturated fat intakes that were below 11% of total energy intake, compared with 3 children at baseline.

In the oldest child with severe CRI (52), increasing energy intake was unsuccessful, despite introduction of a supplement. Attempts to increase energy from foods also failed, with a substantial reported reduction in energy from sugars over the study period, although a modest increase in energy from fats was observed. Child 67 improved his energy intake from solids rather than supplements, which was associated with an increase in total fat and sugars as recommended. The improvement in energy intake in child 54 was predominantly associated with an increase in sugars in the first year and total fat intake in the second year, although saturated fat intake fell. Five children at the end of the study had saturated fat intakes that fell within the recommendations, compared with 3 at baseline. Child 49 was the only one to have a sugar intake that exceeded 30% total energy intake at the end of the study, compared with 3 children at baseline. Two of these 3 children with severe CRI had been known to the dietitian for longer than any of the other children.

Median total fat intake for the cohort as a whole changed very little (baseline values in Table 5.2.10), but this encompassed a non-significant reduction in total fat intake in those with mild and moderate CRI, and an increase in those with severe CRI (Table 6.3.4). Significant changes in saturated fat intakes over time were observed, with the greatest reduction being seen in those with mild CRI (median reduction of 2% of total energy intake; $p=0.016$), with little change observed in those with severe CRI. Little change was observed in mono-unsaturated fat intake over the 2-year period for any of the groups. The intake of poly-unsaturated fats however, significantly increased for the cohort as a whole ($p<0.0001$), and was predominantly associated with a median increase in poly-unsaturated fat of approximately 1% of total energy in children with mild CRI. There was an increase in total carbohydrate intake, accompanied by a reduction in sugar intake in those with mild and moderate CRI, and the reverse was observed in those with severe CRI. Changes in total carbohydrate intake and sugars as a percentage of total energy intakes however, were not significant over the 2 year period as analysed by UNIANOVA.

Change in energy intake was significantly positively correlated to a change in protein intake [$R^2=0.09$; $F=4.21$; 2, 89df, $p=0.018$] for the group as a whole, with the greatest correlation existing in those with mild CRI; $y = 10.48x + 0.41$[$R^2=0.19$; $F=3.63$; 2,32df, $p=0.038$]. The relationships between change in energy and total fat or carbohydrate

intakes were not significant. A highly significant inverse correlation however, was observed between change in total fat and carbohydrate intake [R^2=0.84; F=235; 2,88df, p<0.0001].

Individual serum HDL concentrations over the 2 year period and the changes in this variable and other serum lipids in those who completed 1 and 2 years of the study are depicted for each group of CRI in Figure 6.3 and Tables 6.3.5 - 6.3.7 respectively (appendix 3). As the serum samples obtained were not from children in the fasted state, assessment of individual changes in triglyceride concentrations was not attempted. In children with mild CRI, a reduction in cholesterol was obtained in 7, and an increase in 9 children by the end of the study, which did not seem to relate to the reported change in energy or saturated fat intake. HDL concentrations reduced in 12 children and only increased in 3 children by the end of the study. At baseline, only one child (7) had a HDL concentration below 1 mmol/l, whereas by the end of the study, 3 children, including child 7, exhibited low HDL concentrations. The ratio of total: HDL cholesterol reduced in 7 children but increased in 8.

In the moderate group, 10 children exhibited a reduction in serum total cholesterol, whereas 8 had an increase by the end of the study. At baseline, no child exhibited a low HDL cholesterol (Table 5.3.17, appendix 2), but 2 children demonstrated concentrations below 1 mmol/l by the end of the study (Table 6.3.6, appendix 3). One of these children (28) also reported a substantial increase in energy intake during the study, predominantly associated with the introduction of a glucose polymer. The other child (44) was the only other to be in receipt of a glucose polymer after baseline, although there were concerns that she was struggling to adhere to the prescription. She reported a substantial increase in saturated fat and reduction in carbohydrate intake during the study period. The total: HDL cholesterol ratio was only lower at the end of the study in 3 children with moderate CRI, the remainder demonstrating an increase.

Nine children with severe CRI exhibited a reduction in total cholesterol during the study, compared with only 4 children where an increase was observed. Three children had low HDL cholesterol concentrations at baseline (49, 50 and 59), which became 4 by the end of the study, and of which only one of the children's HDL cholesterol values had been low initially (50) (Table 5.3.18, appendix 2). Child 49 demonstrated a substantial increase in HDL cholesterol (Table 6.3.7, appendix 3). This child reported

an overall increase in total energy intake, but a reduction in energy derived from supplements. This was reflected by a reported increase in intake of sugars, but it could be argued that a glucose polymer should be considered as refined carbohydrate. The other child to demonstrate a substantial improvement in HDL cholesterol was in child 67, which again was a situation where energy intake improved, accompanied by a reduction in intake from nutritional supplements. The substantial reductions in HDL cholesterol in children 58, 60 and 62 were more likely to be associated with the particularly high concentrations recorded at baseline. Total: HDL cholesterol ratio reduced in 7 children and increased in 6 children with severe CRI by the end of the study.

Changes in serum lipid concentrations over the two year period varied, depending upon the severity of renal failure, so that for the cohort as a whole, the only change that proved to be significant was that for HDL cholesterol, with an average reduction of 0.2 mmol/l by the end of the two year period (Table 6.3.8). When analysed by groups, those with both mild and moderate CRI showed a significant reduction in HDL cholesterol, whereas the change was not significant for those with severe CRI. A significant difference in change between the groups over time was noted for total cholesterol, with those with severe CRI exhibiting a significant reduction in total serum cholesterol over the two year period (median 0.8 mmol/l). Little change was observed in total cholesterol for those with mild or moderate CRI. For those with moderate CRI however, a significant increase over time was observed in the total serum cholesterol to HDL cholesterol ratio, with a median increase of 0.6 by the end of the two year period. This was not significant for either of the other two groups. Little change in serum triglyceride concentrations was observed for any of the groups during the two year period.

Table 6.3.4 Comparison of changes from baseline in fat and carbohydrate intakes (inclusive of supplements) in those who completed 1 & 2 years of the study in relation to severity of CRI

Change in nutrient Median (interquartile range)		**All** (N= 50; 42)*	**Mild** (N= 19; 16)*	**Moderate** (N= 18; 16)*	**Severe** (N= 13; 10)*
Total fat (% EAR)	Year 1	0 (-3.2 – 3.9)	-0.7 (-3.3 – 4)	0 (-5.5 – 4.2)	1.6 (-0.6 – 4.4)
	Year 2	-0.8 (-4.8 – 3)	-0.2 (-3.7 – 2.3)	-2.8 (-7.4 – 1.0)	2.8 (-4.8 – 8.8)
Significance		[F=0.2; 1df, p=0.665]	[F=0; 1df, p=0.915]	[F=2.4; 1df, p=0.134]	[F=2.9; 1df, p=0.104]
Saturated fat (% energy)	Year 1	-1.1 (-2.7 – 1.4)	-2.2 (-4.1 – 1.1)	-1.4 (-3.6 – 2.4)	0.2 (-1.2 – 3.3)
	Year 2	-1.5 (-4.1 – 1.0)	-2.0 (-5.0 – 1.3)	-1.7 (-4.2 – 0.6)	-0.3 (-2.5 – 3.5)
Significance		[F=10.6; 1df, p=0.002	[F=6.4; 1df, p=0.016]	[F=3.9; 1df, p=0.057]	[F=0; 1df, p=0.988]
Mono-unsaturated fat	Year 1	0.2 (-0.7 – 2.1)	0.1 (-0.8 – 0.6)	0.8 (-0.9 – 2.6)	1.1 (-2.0 – 2.0)
(% energy)	Year 2	0.3 (-2.2 – 2.5)	0.3 (-1.2 – 1.0)	-0.3 (-3.6 – 2.3)	3.0 (-2.5 – 4.9)
Significance		[F=0.6; 1df, p=0.431]	[F=0; 1df, p=0.934]	[F=0.1; 1df, p=0.737]	[F=1.7; 1df, p=0.206]
Poly-unsaturated fat	Year 1	0.9 (-0.2 – 2.2)	0.9 (0.2 – 2.7)	0.7 (-0.4 – 2.4)	0.8 (-2.1 – 1.9)
(% energy)	Year 2	1.0 (0.0 – 2.4)	1.2 (0.7 – 2.5)	0.8 (-0.4 – 2.2)	1.0 (-2.8 – 4.0)
Significance		[F=15.5;1df, p<0.001]	[F=14.9;1df, p<0.001]	[F=2.0; 1df, p=0.168]	[F=4.0; 1df, p=0.059]
Carbohydrate (% energy)	Year 1	-0.1(-4.5 – 4.1)	1.0 (-2.4 – 4.6)	0 (-5.4 – 4.6)	-2 (-6.5 – 1.5)
	Year 2	1.9 (-3.9 – 4.4)	1.1 (-2.5 – 2.4)	3.3 (-0.4 – 8.1)	-2 (-8.1 – 4.0)
Significance		[F=0.4; 1df, p=0.557]	[F=0; 1df, p=0.987]	[F=2.2; 1df, p=0.148]	[F=1.2; 1df, p=0.278]
Sugar (% energy)	Year 1	0.1 (-4.0 – 4.1)	-0.3 (-2.4 – 4.6)	-1.3 (-6.2 – 3.4)	0.9 (-3.2 – 4.9)
	Year 2	-1.5 (-4.6 – 2.7)	-2.5 (-6.6 – 2.2)	-1.5 (-5.4 – 3.1)	1.4 (-0.7 – 3.6)
Significance		[F=2.8; 1df, p=0.100]	[F=3.5; 1df, p=0.070]	[F=0.4; 1df, p=0.534]	[F=0; 1df, p=0.854]

*N= (Year 1; Year 2); EAR, expected average requirement;
Significance is determined by UNIANOVA for changes over time, observations made at 6 monthly intervals for 2 yrs

Table 6.3.8 Comparison of changes in serum lipid concentrations in those who completed 1 & 2 years of the study in relation to severity of CRI

Change in variable Median (interquartile range)		**All** (N= 54; 50)*	**Mild** (N= 20; 18)*	**Moderate** (N= 20; 19)*	**Severe** (N= 14; 13)*
Total cholesterol (mmol/l)	Year 1	-0.05 (-0.33 – 0.3)	-0.1 (-0.4 – 0.1)	0.15 (-0.38 – 0.38)	-0.1 (-0.3 – 0.25)
	Year 2	-0.1 (-0.7 – 0.38)	0 (-0.3 – 0.18)	-0.1 (-0.7 – 0.7)	-0.8 (-1.15 – 0.35)
Significance		[F=0.8; 1df, p=0.371]	[F=0; 1df, p=0.941]	[F=0.7; 1df, p=0.418]	[F=7.8; 1df, p=0.007]
HDL cholesterol (mmol/l)	Year 1	-0.1 (-0.4 – 0)	-0.2 (-0.4 – 0)	-0.1 (-0.18 – 0)	-0.1 (-0.55– 0.28)
	Year 2	-0.2 (-0.3 – 0)	-0.1 (-0.28 – 0)	-0.2 (-0.3 – -0.1)	-0.2 (-0.4 – 0.23)
Significance		[F=11.7;1df, p=0.001]	[F=5.3; 1df, p=0.025]	[F=9.8; 1df, p=0.003]	[F=0.5; 1df, p=0.465]
Total: HDL cholesterol	Year 1	0.26 (-0.12 – 0.67)	0.5 (-0.02 – 0.77)	0.22 (-0.12 – 0.67)	-0.03 (-0.88 – 0.75)
	Year 2	0.28 (-0.19 – 0.84)	0.25 (-0.34 – 0.8)	0.6 (0.1 – 1.14)	-0.13 (-0.6 – 0.69)
Significance		[F=3.6; 1df, p=0.060]	[F=2; 1df, p=0.165]	[F=7.5; 1df, p=0.008]	[F=0.5; 1df, p=0.496]
Triglycerides (mmol/l)	Year 1	0.1 (-0.2 – 0.5)	0.05 (-0.2 – 0.58)	0.2 (-0.28 – 0.5)	-0.1 (-0.25 – 0.25)
	Year 2	0.1 (-0.35 – 0.4)	0 (-0.7 – 0.35)	0.2 (0 – 0.5)	-0.1 (-0.85 – 0.4)
Significance		[F=1.1; 1df, p=0.300]	[F=1.9; 1df, p=0.169]	[F=0.7; 1df, p=0.394]	[F=2; 1df, p=0.164]

*N= (Year 1; Year 2)

Significance is determined by UNIANOVA for changes over time, observations made at 6 monthly intervals for 2 yrs

6.4 Progression of CRI

Progression of CRI is ideally determined by measuring clearance of a non-metabolised substance from plasma, such as the ^{51}Cr-EDTA method used for establishing baseline GFR's in this study (Chapter 4). Unfortunately this method was not used to confirm final GFR values at the end of the study. Other biochemical markers such as plasma creatinine give an indication of progression (creatinine/ height being used to estimate progression in children). Plasma urea is used in clinical practice as a rough guide in assessing whether protein intake is adequate, or exceeds that recommended, in which case it could potentially contribute to progression (section 1.3.4). High dietary phosphate intakes have also been linked with progression (section 1.3.4), as has raised blood pressure (section 1.3.1) and high sodium intakes (section 1.3.2), and the presence of substantial proteinuria (section 1.3.3). Although sodium intakes are referred to in this section, they are tabled in section 6.5, due to the practicalities of grouping nutrient data together for tabling.

6.4.1 Plasma urea and electrolytes

Changes in individual plasma creatinine, urea, potassium and bicarbonate concentrations in those who completed 1 and 2 years of the study are depicted for each group of CRI in Tables 6.4.1.1-6.4.1.3 (appendix 3). The most marked reductions in plasma urea concentrations occurred in children 4 and 24. Child 4 reported a substantial increase in energy intake, which was not accompanied by a similar increase in protein intake, such that the percentage of energy derived from protein reduced (Table 6.2.2.1, appendix 3). This child demonstrated an increase in BMI SDS during the study (Table 6.2.1.1, appendix 3). Child 24 was the only one in receipt of an energy supplement, the amount of energy from which over the course of the study was reported to fall, resulting in an increase in percentage of energy from protein. Despite this, energy intake was maintained and child 24 exhibited a substantial increase in height and weight SDS during the study. In some children who exhibited a reduction in plasma urea, an improvement in height SDS was observed (6, 9, 18, 25), whereas for other children it was accompanied by an increase in weight SDS (10,19). In all these children, protein intake was reported to be lower, compared with baseline. Children 13 and 23 reported notable increases in plasma urea, but there was no apparent pattern between these 2

children, with one gaining growth and the other losing BMI SDS, and one reducing their percentage energy from protein while the other increased their intake.

In those with moderate CRI, there was also no clear picture between changes in protein intake, growth and plasma urea concentrations, including that for child 35, who exhibited a substantial increase in plasma urea concentration during the study period. The greatest increase however, was at year one, where a large increase in protein as a percentage of energy was reported, alongside an increase in protein per kg body weight (Table 6.2.2.2, appendix 3). This was reported to have reduced during the second year. Child 28 who commenced energy supplements however, did exhibit a reduction in plasma urea concentrations, accompanied by a substantial reported reduction in percentage of energy from protein and a large increase in BMI SDS. The large increase in protein intake in child 37 however, associated with an improvement in appetite and cessation of supplements, did not result in a substantial increase in plasma urea.

At baseline, all but one child (58) with severe CRI had a plasma urea concentration above 10 mmol/l, but by the end of the study 3 children (50, 58 and 65) had values below this. Child 50, who exhibited a substantial reduction in plasma urea, reported a significant reduction in energy and protein intake, which was felt to be associated with over-reporting at baseline, as growth improved during the study (Table 6.2.2.3, appendix 3). A reduction in protein intake however, may have occurred. Child 58 was able to reduce her reported protein intake to 1.5 g/kg by the end of the first year, which involved a reduction in percentage energy derived from protein. The only child in the study to exhibit a reduction in plasma creatinine concentration (65) was the one with developing anorexia nervosa, which was therefore accompanied by a reduction in all nutrient intakes and loss in weight and BMI SDS. A substantial increase in plasma urea occurred in child 49, who reported a reduction in energy derived from supplements, such that an increase in protein intake and percentage of energy from protein occurred. Loss of weight and BMI SDS ensued during the second year in this child.

The majority of children throughout the study demonstrated plasma potassium concentrations that fell within the normal range. Of the 3 children with moderate CRI that exhibited plasma potassium concentrations that exceeded 5.3 mmol/l at 2 years, one was in receipt of an ACEI and no child was deemed to be acidotic. The value for child

42 was likely to have been spurious. Only 2 children with severe CRI had high plasma potassium concentrations and both were in receipt of an ACEI. Child 63 exhibited such raised potassium concentrations that his antihypertensive medication was changed. Both children had been advised to reduce their dietary potassium intakes.

Only children with severe CRI exhibited low plasma bicarbonate concentrations. Six children were prescribed sodium bicarbonate at recruitment, and 3 children remained on the medication for the 2 year period, the other 3 entering the ESRD programme. All these children demonstrated plasma bicarbonate concentrations above 18 mmol/l. Only one child (53) exhibited sub-optimal plasma bicarbonate concentrations throughout the study, and had not been prescribed sodium bicarbonate. This child had not reached the pubertal stage and appeared to lose height SDS during the study, although was able to increase BMI SDS during the second year. He reported more than an adequate energy intake at baseline, but a large reduction in energy intake was reported at the end of the 2 years. This may have been a consequence of over-reporting at baseline.

Median changes in plasma concentrations of specific electrolytes and metabolites over the 2 year period, are illustrated in table 6.4.1.4. Significant differences in change in plasma creatinine concentrations over time between groups were observed, with larger increases in plasma creatinine concentration being associated with increasing severity of CRI. UNIANOVA was repeated for the variable plasma creatinine/ height, to account for the growth-related increase in creatinine associated with greater muscle mass, but the results were similar to that illustrated. Plasma urea concentrations did not change significantly over time for the cohort as a whole, or for any group of CRI. An increase in plasma urea was noted in those with severe CRI (median 3.4 mmol/l), whereas a slight reduction was observed in those with mild and moderate CRI. There was little correlation between change in protein intake when described either in g/kg or as percentage of energy from protein and plasma urea concentration, for the cohort as a whole or for any of the groups individually.

Little change in median plasma potassium concentration was observed during the two year period for the cohort as a whole, although the changes over time were significant by UNIANOVA. Both children with moderate and severe CRI exhibited a median increase in plasma potassium concentrations which, although higher for those with

severe CRI, was only significant in the moderate group, probably due to the greater inter-individual variation and smaller number of observations in children with severe CRI. Plasma bicarbonate concentrations increased by a median of 2 mmol/l for the cohort as a whole over the two year period and this change was considered to be highly significant by UNIANOVA. Children with mild and moderate CRI exhibited a significant increase in plasma bicarbonate concentrations over time, whereas those with severe CRI did not, despite the use of bicarbonate supplements in this group. Explanations for this were not apparent and were not explored in great depth, due to issues surrounding acid-base balance falling outside the remit of this study.

6.4.2 Blood pressure related to sodium intake

Individual systolic and diastolic blood pressure SDS's over the 2 year period and the changes in these parameters in those who completed 1 and 2 years of the study are depicted for each group of CRI in Figures 6.4.2.1 – 6.4.2.2 and Tables 6.4.2.1 - 6.4.2.3 respectively (appendix 3). An overall reduction from 52% to 30% of children with a SBP above or equal to 120 mmHg occurred by the end of the 2 year period (mild, 40% to 22%; moderate, 50% to 42%; severe 68% to 23%). This was associated with a reduction of approximately 50% in the number of children with a SBP $\geq$ 2 SDS (mild, 24% to 11%; moderate, 28% to 11%; severe, 47% to 25%). For DBP SDS, unlike the other two groups, an increase was observed in those with moderate CRI, from 17% children with a DBP $\geq$ 2 SDS at baseline to 28% at two years, such that at the end of the study, 56% of those with raised DBP had moderate CRI, and 33% severe CRI.

Seven children with both mild and moderate CRI showed a substantial improvement in SBP SDS (> -1 SDS), which was also accompanied by an improvement in DBP SDS in the majority. In those with mild CRI, 2 children (9, 23) were in receipt of anti-hypertensive agents from the outset (Table 6.1.5). Child 23 exhibited a substantial drop in both SBP and DBP one year into the study, despite no change in her small dose of ACEI and proteinuria status at that time-point. She did however, successfully reduce her dietary sodium intake by approximately 35 mmol/ d compared with baseline (Table 6.5.1, appendix 3). Child 9 unfortunately did not provide follow-up food diaries for analysis. Of the other children with mild CRI who exhibited a reduction in SBP and DBP, children 10, 19 and 27 reported lower sodium intakes compared to baseline,

whilst children 1, 4 and 17 reported an increase in sodium intake during the study. Child 1 however, still had a sodium intake that was below that recommended of 100 mmol/d. One child (26) with mild CRI exhibited a substantial increase in DBP SDS, despite a reduction in sodium intake, and was commenced on an ACEI 18 months into the study, in association with increasing proteinuria (Table 6.1.1). Of the 6 children who demonstrated an increase in SBP, all but one child had increased their sodium intake over the study period. There appeared to be a less clear relationship however, between changes in sodium intake and changes in DBP in mild CRI.

Of the 7 with moderate CRI who showed a substantial improvement in SBP SDS (> -1 SDS), only one of the children (39) was prescribed an antihypertensive, and this was only for the first year of the study (Table 6.1.6). This child however, reported an increase in sodium intake during the second year (Table 6.5.2, appendix 3). Of the others, children 29, 40, 42 and 45 reported reduced sodium intakes and children 31 and 44 an increase in intake, although child 44 still had a sodium intake that was below 100 mmol/d. Three children with moderate CRI (31, 32, and 46) exhibited a substantial increase in DBP SDS, which was not matched by an increase in SBP SDS. In both cases where subsequent food diaries were completed, sodium intake was reported to have increased, although in one child this remained within the recommended limit. Only one child (28) with moderate CRI showed a substantial increase in SBP SDS, which was accompanied by an increase in reported dietary sodium. The only child (43) with moderate CRI to be prescribed an anti-hypertensive other than an ACEI (β-blocker in this case), continued to have raised blood pressure during the study period, despite a reported reduction in sodium intake. Prescription of an antihypertensive was predominantly an ACEI, associated with the presence of substantial proteinuria, in all but one of the 5 children with moderate CRI.

Six of the 12 children with severe CRI for whom SDS's could be obtained, exhibited a substantial improvement in SBP SDS, of which 4 children also showed a substantial improvement in DBP SDS (Table 6.4.2.3, appendix 3). In these 6 children, in 4 out of 5 cases where food diaries were available, reported dietary sodium intakes were lower compared with baseline (Table 6.5.3, appendix 3). Four of these 6 children were also prescribed antihypertensives; ACEI alone in all cases apart from one child (63), who was changed onto a β-blocker after 18 months, associated with raised plasma potassium

concentrations. Following this change, an improvement in SBP SDS was observed. One of the children (62) not prescribed antihypertensives who exhibited a substantial reduction in SBP and dietary sodium intake however, was in receipt of sodium bicarbonate, which would confound any potential benefit from a reduction in dietary sodium. 50% of children with severe CRI who exhibited substantial proteinuria and who completed the 2 year study were in receipt of an ACEI (Tables 6.1.3 & 6.1.7). For the 3 children with severe CRI on a combination of antihypertensives, DBP SDS increased in one child (65) and both SBP and DBP remained above that desired in the other two (57, 60). Two children (49, 65) with severe CRI exhibited a substantial increase in DBP SDS by the end of the study, and one child (54) an increase in SBP SDS, which were accompanied by an increase in reported dietary sodium in two (49, 54).

Systolic blood pressure SDS fell over time, with a mean reduction of 0.7 SDS at the end of the two year period (Table 6.4.2.4). The change in DBP SDS was much smaller, with a mean change for the whole group of 0.3 SDS. The change in SBP SDS over time was deemed to be highly significant by UNIANOVA, for the whole group and at each level of severity of CRI. For the cohort as a whole, the reduction in DBP SDS also proved to be significant, but the differences were not significant for any of the individual groups. By the end of the study, 15% of all children had a SBP, and 19% a DBP $\geq$ 2 SDS ($\geq$ 95th percentile). Systolic and diastolic BP conversions to SDS provided discreet data only, which may impact upon the sensitivity of these results. No correlation between systolic or diastolic blood pressure and deterioration in GFR was found. Comparisons drawn between the children that did and did not complete the 2 year study at baseline also suggested that there were no differences between the 2 groups for SBP in children with mild CRI. For SBP in those with severe CRI however, the children who did not complete the study exhibited almost double the mean SBP SDS compared with those remaining (Table 6.1.4). A greater mean DBP SDS in both those with mild and severe CRI was also noted in the children failing to complete the study, compared with those who finished the study. Unfortunately, both the 2 children with moderate CRI were too young to determine BP SDS's.

Individual sodium intakes over the 2 year period and the changes in these variables in those who completed 1 and 2 years of the study are depicted for each group of CRI in

Figures 6.5.1 and Tables 6.5.1-6.5.3 respectively (appendix 3). By the end of the study, 5 (26%) children with mild CRI, 6 (32%) with moderate and 9 (69%) with severe CRI had total sodium intakes below the target 100 mmol/d, compared with 10 (40%), 11 (56%) and 7 (39%) at baseline. Total sodium intakes significantly increased (p=0.014), as analysed by UNIANOVA, for the cohort as a whole by the end of the 2 year period (median of 10 mmol/d) (Table 6.5.4). When analysed between groups, the increase in sodium intake (mmol/d) over the two year period was only significant for those with mild CRI (p=0.037). Due to the relationship between total energy intake and sodium intake (mmol/d) (Figure 5.2.2), sodium intake was expressed as a percentage of total energy intake, to observe the change in sodium intake attributed to energy intake over the two year period. When sodium intake was expressed in this manner, there was no significant change for the cohort as a whole [F=2.01; 1df, p=0.162], but a significant change with time did occur in those with mild CRI [F=4.54; 1df, p=0.04], suggesting that sodium intake increased out of proportion to the rise in energy intake. This relationship did not exist in the other two groups of renal failure.

For the cohort as a whole, change in sodium intake was significantly correlated to change in SBP SDS (Figure 6.4.2.3a), but not DBP SDS (Figure 6.4.2.3b). For those with mild CRI, 18% of the variation in SBP could be ascribed to a change in sodium intake. This relationship did not appear to exist in the more severe groups of CRI. The pattern of correlation between the groups for DBP SDS and sodium intake was markedly different (Figure 6.4.2.4b), with the only apparent relationship occurring in those with severe CRI, where 23% of the variation in DBP SDS could be attributed to a change in total sodium intake. This relationship however, was not regarded to be significant. If sodium intake was expressed in relation to body weight however, a highly significant relationship was observed, where 52% of the variation in DBP SDS could be ascribed to a change in sodium intake in those with severe CRI [R^2=0.52; F=9.37; 2,17df, P=0.002]. These findings would support the changes noted previously for individuals, where in mild CRI, the majority of children who reported an increase in dietary sodium intake exhibited an increase in SBP and over half the children who reduced their intake were able to lower their SBP. A clear relationship was not apparent for DBP in this group. In the severe group however, the relationship between dietary sodium intake and blood pressure appeared to be more consistent for both SBP and DBP, although a correlation was not noted for SBP. The correlation also did not

support the general pattern observed between change in sodium intake and BP in those with moderate CRI.

In contrast to the lack of correlation that seemed to exist between change in BP and change in renal function, a significant inverse association between total sodium intake and change in GFR over the two year period was observed in children with mild CRI (Figure 6.4.2.4 a), where 20% of the variation in GFR could be attributed to total sodium intake, with the equation y= -0.125x +9.57. This is supported by the observation that of the 5 children with mild CRI who exhibited the greatest reductions in estimated GFR (-19 to –23, as depicted in Table 4.3.5.2, appendix 1), 4 of the children reported substantial increases in sodium intake, and final sodium intakes were above 100 mmol/d in all 5 children. A relationship between individual changes in GFR and phosphate intakes was also evident. Although only 2 of the 5 children reported substantial increases in phosphate intake, of the 8 children who reported final phosphate intakes within the target range, only 1 child exhibited a reduction in GFR of more than 8 ml/min/ 1.73m^2, and 50% of the children exhibited minimal changes in GFR, ranging from +3 to -3 ml/min/ 1.73m^2. As a result, a correlation between the two variables was observed, albeit non-significant, where 16% of the variation in GFR could be attributed to total phosphate intake, with the equation y= -0.02x +13.91, an association not evident in children with more severe renal failure (Figure 6.4.2.4 b).

6.4.3 Proteinuria

The degree of proteinuria changed little over the two year period, as illustrated by the lack of change in the urine protein: creatinine ratio for the cohort as a whole. One child with mild CRI demonstrated an improvement in proteinuria, and was not prescribed an ACEI, whereas 2 children with moderate CRI demonstrated an improvement, of which one was associated with an ACEI. In those with severe CRI, 3 children exhibited a substantial improvement in proteinuria, of which only one was prescribed an ACEI. Comparison between change in proteinuria and estimated GFR was non-significant due to the lack of substantial change in proteinuria, whereas a correlation between change in estimated GFR and actual degree of proteinuria was more meaningful, using forced stepwise linear regression which takes the effect of time into account (Figure 6.4.3). A significant correlation between the degree of proteinuria and change in estimated GFR was found for the cohort as a whole, of which approximately half of the relationship

could be attributed to the effect of time on change in renal function. When assessed by each group, there was no correlation in those with mild CRI, but highly significant correlations were noted between the absolute urine protein to creatinine ratio and change in estimated GFR in those with moderate and severe CRI. In children with moderate CRI, 33% of the variation in renal function could be attributed to a change in proteinuria. For those with severe CRI, the majority of the deterioration in renal function was due to an effect of time (R^2=0.24), rather than degree of proteinuria.

Prescription of an ACEI did not appear to be consistent across the groups. Of the 3 children with mild CRI with substantial proteinuria, 2 of the 3 children were prescribed an ACEI. Although a similar proportion of children with moderate and severe CRI who completed the 2 year study exhibited proteinuria (Tables 6.1.2 & 6.1.3), 7 children with moderate CRI had proteinuria who were not in receipt of an ACEI, whereas only 3 with severe CRI were not prescribed an ACEI (Tables 6.1.6 & 6.1.7). It was also interesting to note the comparisons drawn regarding baseline proteinuria, between the children that did and did not complete the 2 year study. There were no differences in children with mild CRI, whereas the only child to reach the ESRD programme with moderate CRI had the highest degree of proteinuria within the group, and all 6 children with severe CRI who reached ESRD exhibited substantial proteinuria, the mean being twice that of those remaining within the study (Table 6.1.4).

Table 6.4.1.4 Comparison of changes in plasma concentrations of relevant electrolytes and metabolites in those who completed 1 & 2 years of the study in relation to severity of CRI

Change in variable Median (interquartile range)		All (N= 54; 50)*	Mild (N= 20; 18)*	Moderate (N= 20; 19)*	Severe (N= 14; 13)*
Creatinine (μmol/l)	Year 1	11.5 (4 – 26.5)	6.5 (2.5 – 18.8)	15 (4 – 32)	15 (4.3 – 35.8)
	Year 2	25 (12.5 – 50.3)	14 (8 – 27.8)	29 (15 – 48)	71 (32 – 139.5)
Significance		[F=247; 1df, p<0.001]	[F=97; 1df, p<0.001]	[F=94; 1df, p<0.001]	[F=67; 1df, p<0.001]
Urea (mmol/l)	Year 1	-0.5 (-1.8 – 0.8)	-0.2 (-1.8 – 0.9)	-0.8 (-1.8 – 0.1)	-0.1 (-2.3 – 3.1)
	Year 2	0.2 (-1.8 – 2)	-0.1 (-1.8 – 0.8)	-0.6 (-1.8 – 1.8)	3.4 (-2.7 – 6)
Significance		[F=0; 1df, p=0.607]	[F=3; 1df, p=0.113]	[F=0; 1df, p=0.665]	[F=2; 1df, p=0.161]
Potassium (mmol/l)	Year 1	0 (-0.2 – 0.3)	-0.1 (-0.2 – 0.3)	-0.1 (-0.2 – 0.3)	0.2 (-0.3 – 0.4)
	Year 2	0 (-0.3 – 0.5)	-0.1 (-0.2 – 0.2)	0.1 (-0.3 – 0.5)	0.3 (-0.5 – 0.8)
Significance		[F=5; 1df, p=0.030]	[F=0; 1df, p=0.884]	[F=4; 1df, p=0.047]	[F=3; 1df, p=0.104]
Bicarbonate (mmol/l)	Year 1	2 (0 – 4.5)	2 (1 - 6)	1.5 (0 – 4.8)	2 (-0.8 – 4.3)
	Year 2	2 (0 – 4.5)	3 (0.5 - 5)	1 (0 - 5)	0 (-2 – 2.5)
Significance		[F=12; 1df, p=0.001]	[F=8; 1df, p=0.005]	[F=14; 1df, p<0.0001]	[F=0; 1df, p=0.994]

*N= (Year 1; Year 2)

Significance is determined by UNIANOVA for changes over time, observations made at 6 monthly intervals for 2 yrs

Table 6.4.2.4 Comparison of mean change in blood pressure SDS in those completing 1 & 2 years of the study in relation to severity of CRI

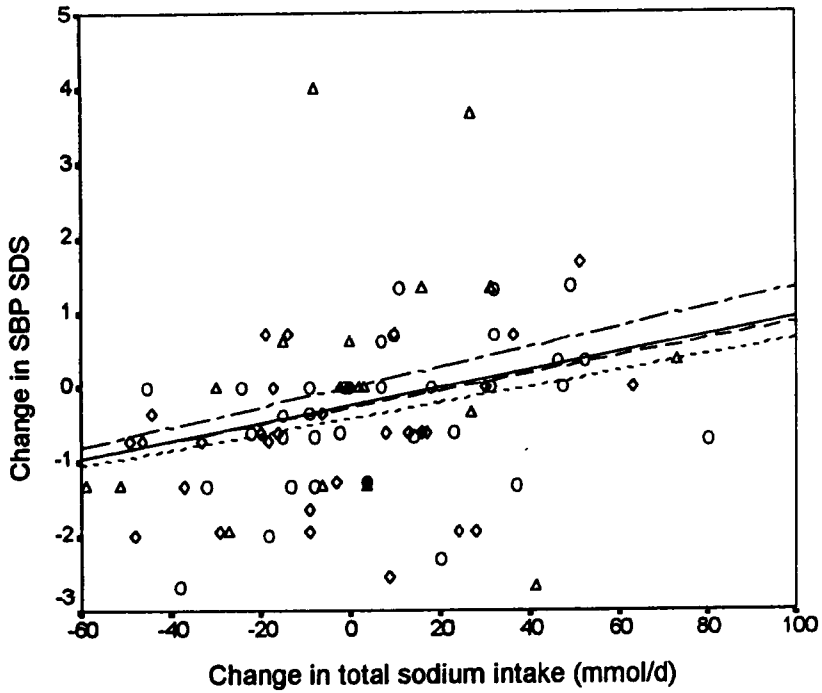
Mean change (SD)		All (n=50;48)*	Mild CRI (n=20;18)*	Moderate CRI (n=18; 18)*	Severe CRI (n=12; 12)*
Systolic BP					
SDS	1 yr	-0.4 (0.9)	-0.3 (0.9)	-0.6 (0.9)	-0.3 (1.1)
	2 yr	-0.7 (1.1)	-0.6 (1.1)	-0.7 (1.1)	-0.9 (1.3)
Significance		[F=24.77; 1df, p<0.0001]	[F=8.98; 1df, p=0.004]	[F=7.34; 1df, p=0.008]	[F=8.40; 1df, p=0.006]
Diastolic BP					
SDS	1 yr	-0.2 (1.0)	-0.4 (1.1)	-0.1 (0.8)	0.0 (0.9)
	2 yr	-0.3 (1.4)	-0.5 (1.4)	-0.1 (1.2)	-0.3 (1.8)
Significance		[F=4.77; 1df, p=0.030]	[F=3.28; 1df, p=0.074]	[F=0.26; 1df, p=0.612]	[F=1.49; 1df, p=0.228]

*N= (1 year; 2 year); BP, blood pressure; SDS, standard deviation score

Significance is determined by UNIANOVA for changes over time, observations made at 6 monthly intervals for 2 yrs

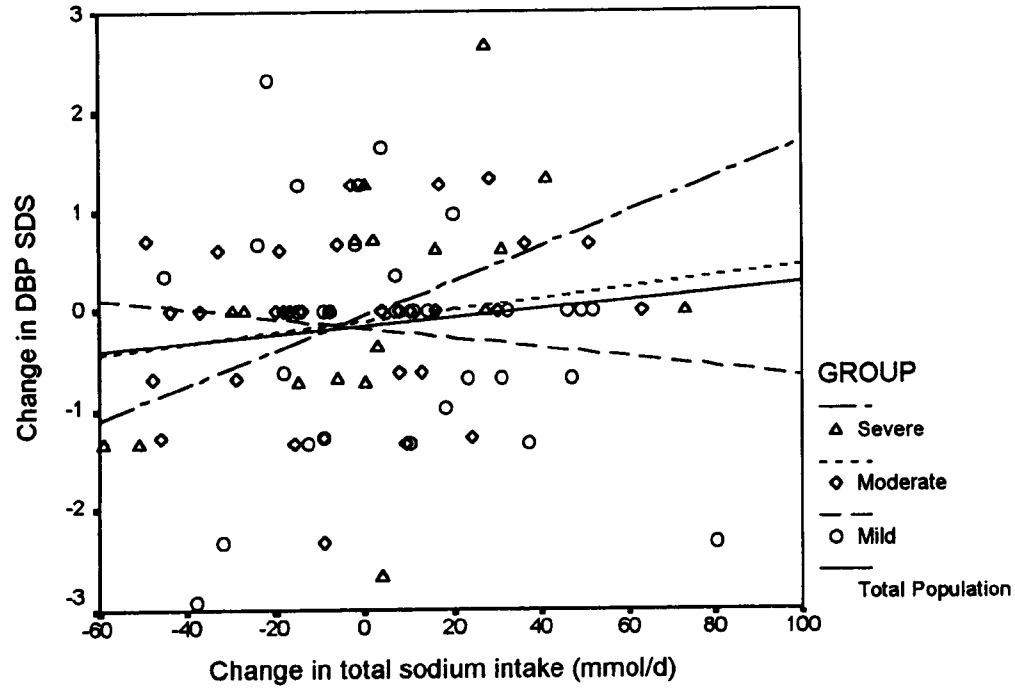
Figure 6.4.2.3 Correlation between change in sodium intake and change in a) systolic b) diastolic blood pressure SDS for each group

a)



Total [R^2=0.10; F=4.44; 2,81df, P=0.015]
Mild CRI [R^2=0.18; F=3.20; 2,30df, P=0.055]
Moderate CRI [R^2=0.08; F=1.22; 2,28df, P=0.312]
Severe CRI [R^2=0.07; F=0.66; 2,17df, P=0.530]

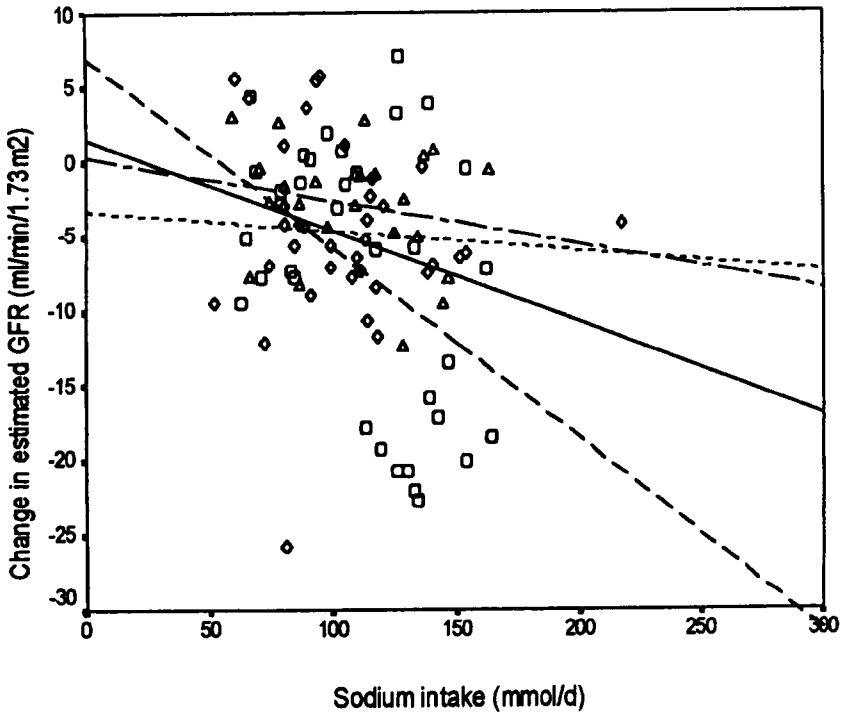
b)



Total [R^2=0.01; F=0.58; 2,81df, P=0.564]
Mild CRI [R^2=0.02; F=0.24; 2,30df, P=0.792]
Moderate CRI [R^2=0.04; F=0.58; 2,28df, P=0.568]
Severe CRI [R^2=0.23; F=2.59; 2,17df, P=0.104]

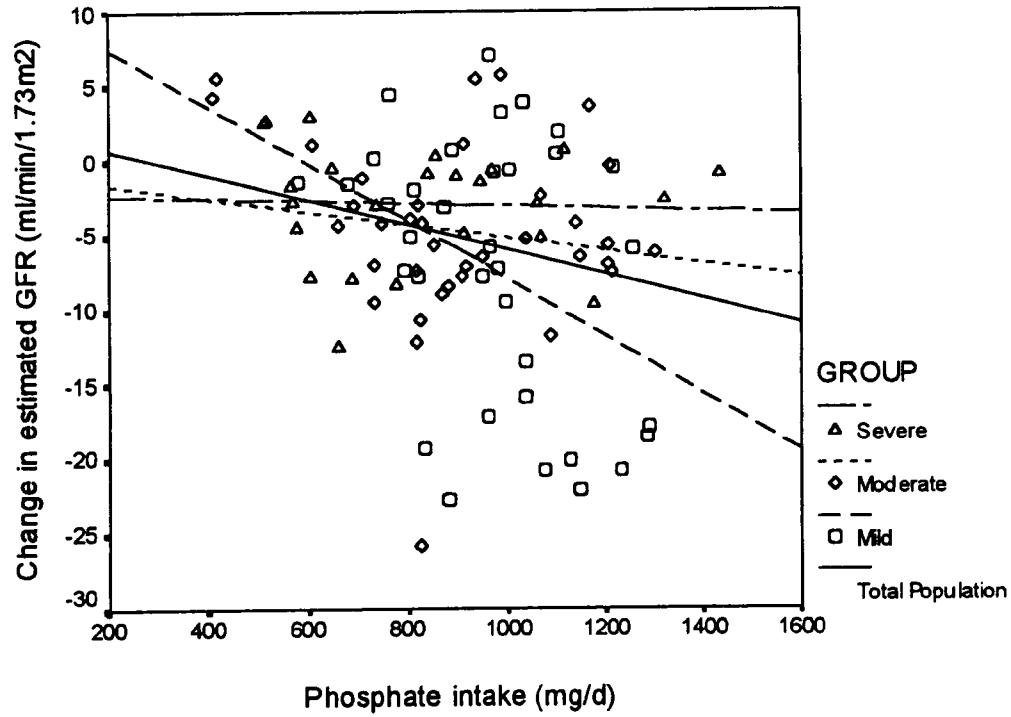
Figure 6.4.2.4 Correlation between change in GFR and a) total sodium intake and b) total phosphate intake between groups

a)



Total [R^2=0.09; F=4.71; 2,92df, P=0.011]
Mild CRI [R^2=0.20; F=3.96; 2,32df, P=0.029]
Moderate CRI [R^2=0.01; F=0.16; 2,33df, P=0.854]
Severe CRI [R^2=0.35; F=5.73; 2,21df, P=0.010]*

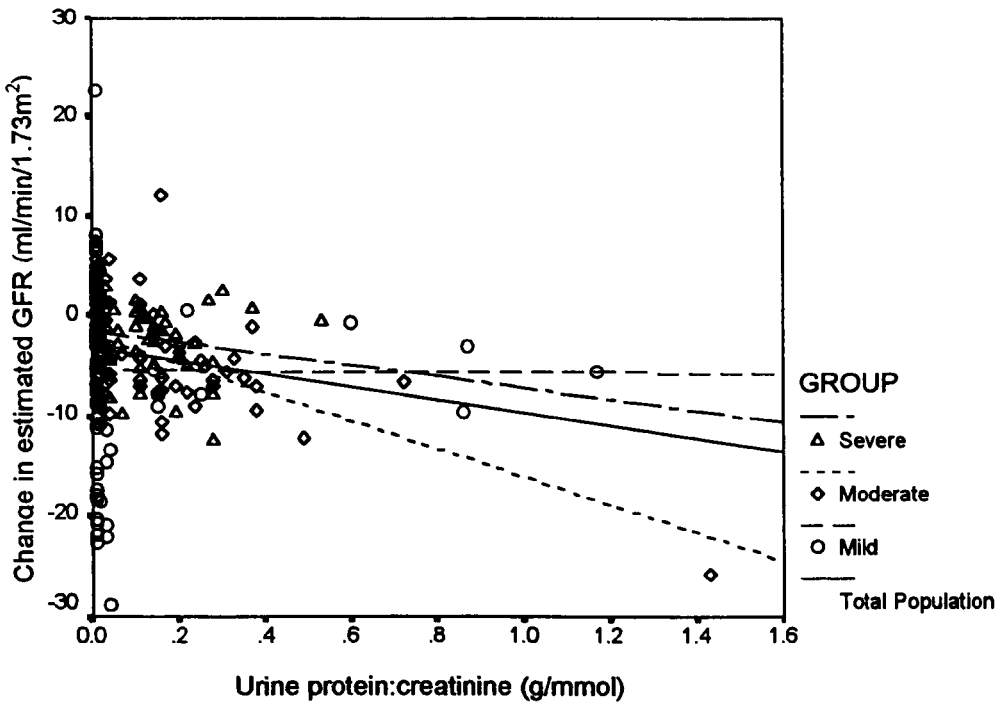
b)



Total [R^2=0.10; F=5.30; 2,92df, P=0.007]
Mild CRI [R^2=0.16; F=3.20; 2,32df, P=0.064]
Moderate CRI [R^2=0.03; F=1.22; 2,33df, P=0.588]
Severe CRI [R^2=0.37; F=0.66; 2,21df, P=0.008]*

* Changes attributed to change in GFR with time, and not associated with total nutrient intake

Figure 6.4.3 Correlation between change in estimated GFR and actual level of proteinuria over the 2 year period between groups



Estimated GFR: (height (cm) x 36/ plasma creatinine (μmol/l)) - 4

Total	[R^2=0.09; F=9.36; 2,198df, P<0.0001]
Mild CRI	[R^2=0.03; F=1.15; 2,65df, P=0.324]
Moderate CRI	[R^2=0.33; F=17.96; 2,74df, P<0.0001]
Severe CRI	[R^2=0.27; F=9.79; 2,53df, P<0.0001]

6.5 Sodium, phosphorus and calcium intakes and bone metabolism

Individual dietary sodium, phosphate and calcium intakes over the 2 year period and the changes in these variables in those who completed 1 and 2 years of the study are depicted for each group of CRI in Figures 6.5.1–6.5.3 and Tables 6.5.1-6.5.3 respectively (appendix 3). Changes in sodium intake during the study have been addressed in relation to blood pressure in the previous chapter. Reduction in phosphate intake was greatest during the first year for the cohort as a whole (median –103 mg/d), but was not sustained during the second year (median –45 mg/d), and as a result, did not reach significance when analysed by UNIANOVA ($p=0.059$) (Table 6.5.4). This pattern was true for those with mild and moderate CRI, but was reversed in those with severe CRI, although the quantity of change in phosphate intake was smaller than in the other two groups. When UNIANOVA was repeated on the change in phosphate intake during the first year of the study only, for the cohort as a whole the change became highly significant ($p<0.0001$). There were no significant differences between groups in change in phosphate intake over the two year period.

In those with mild CRI, 11 children at 1 year reduced their phosphate intake, whereas only 8 children had been able to do so by the end of the study. Ten children (53%) had final phosphate intakes that were below 1000 mg/d, compared with 12 (52%) at baseline i.e. no improvement overall. In the moderate group, the majority of children were able to reduce their phosphate intake for the duration of the study, with only 5 children reporting increased phosphate intakes. Fourteen children (74%) with moderate CRI were able to meet the target phosphate intake of < 1000 mg/d, compared with ten (53%) at baseline. For those with severe CRI, 13 children (72%) at baseline reported acceptable dietary phosphate intakes, which changed to 11 children (85%) by the end of the study.

There was a significant reduction in calcium intake (% RNI) for the cohort as a whole over the 2 year period (Table 6.5.4). This related to changes in children with mild and moderate CRI, with a median reduction of 30-40% RNI for calcium during the second year, whereas those with severe CRI showed little change in intake. This can be related to actual intakes at baseline, as depicted in Tables 5.2.11-5.2.13 (appendix 2). At baseline, 4 (17%) children with mild CRI, 5 (26%) with moderate and 14 (77%)

children with severe CRI had calcium intakes below 100% RNI. Calcium intakes at the end of the study were below 100% RNI in 8 (42%) children with mild, 12 (63%) with moderate and 9 (69%) with severe CRI. Calcium intakes reduced in all but 3 children with mild CRI during the study. The greatest potential detrimental change to calcium intake occurred in those with moderate CRI, where 65% of the group resulted in calcium intakes falling below 80% RNI, which was only the case in 6% of those with mild CRI. Children with severe CRI continued to be represented by approximately 50% of the group having calcium intakes below 80% RNI.

Simple linear regression showed that a change in calcium intake was significantly positively correlated to a change in phosphate intake for the cohort as a whole and between each group (Figure 6.5.4). The most significant correlation existed in those with mild CRI, with the equation $y= 0.145x + 7.4$, where 61% of the variation in calcium intake could be attributed to a change in phosphate intake. Change in dietary phosphate did not correlate with change in protein intake for the cohort as a whole, but was significant for those with moderate CRI [R^2=0.19; F=3.62; 2,31df, p=0.039]. The greatest reductions in phosphate intake in those with severe CRI (50, 53, 63) were associated with substantial reductions in both dietary calcium and protein intakes. This was also the case in moderate CRI (31, 36, 38, 40, 43, 47, 48) and mild CRI (6, 17, 18, 19, 22, 26, 27). Reported dietary phosphate increased in 9 children with mild CRI, yet 5 of these children reported a reduction in calcium intake and only 3 of the 9 children with mild CRI reported an increase in protein intake (g/kg). For moderate CRI, 6 children reported an increase in dietary phosphate. Those children either reported a reduction in protein intake with or without an increase in calcium, a reduction in both calcium and protein intake, a reduction in calcium with an increase in protein, or an increase in calcium and protein. A similar variety of responses occurred in those with severe CRI, where child 54 exhibited a substantial increase in dietary phosphate, associated with a large increase in calcium intake, but decrease in protein intake, whereas child 49 showed little change to calcium intake, but an increase in protein.

Individual plasma concentrations relating to bone activity over the 2 year period and the changes in these variables in those who completed 1 and 2 years of the study are depicted for each group of CRI in Figures 6.5.5–6.5.6 and Tables 6.5.5-6.5.7 respectively (appendix 3). Plasma calcium concentrations did not change significantly

over time for any of the three groups and there were no significant differences between the groups (Table 6.5.8). Plasma phosphate concentrations also did not differ significantly over time for the cohort as a whole or between the various levels of severity of CRI. Twelve (57%) children with mild CRI demonstrated reductions in plasma phosphate during the study, compared with 13 (65%) children with moderate and 8 children (57%) with severe CRI. Only 1 child with mild CRI had a plasma phosphate concentration that exceeded the normal range at baseline, but this was the youngest child (Table 5.3.6, appendix 2). The reference range extends to 2 mmol/l in children up to 3 years of age and 1.8 mmol/l up to 6 years, so that a concentration of 1.74 mmol/l was appropriate for age at baseline, as was the slight increase noted at 2 years. In moderate CRI, all children exhibited normal plasma phosphate concentrations at baseline, whereas 2 children exceeded the normal range by the end of the study. One of these children was child 36, who required dialysis after 1 year. Three children (50, 51, 55) with severe CRI at baseline (Table 5.3.8, appendix 2) had plasma phosphate concentrations that were above the normal range, and by the end of the study 3 children continued to do so, although they were 3 different children. Child 50 who was commenced on alfacalcidol due to a high baseline alkaline phosphatase and above normal serum PTH, also reported a substantial reduction in dietary phosphate intake, and both plasma phosphate and PTH were normalised by the end of the study. This was one of the younger children in the study. Child 51 was in receipt of both alfacalcidol and calcium carbonate at baseline, but there were concerns that this child did not comply well with treatment. Despite that, both plasma phosphate and PTH concentrations improved during the study. Child 55, a male adolescent required dialysis soon after entry into the study. In two of the 3 children who developed raised plasma phosphate concentrations (49, 54 and 66), an increase in PTH concentration was also observed. A PTH value was not available for child 54. This adolescent reported a substantial increase in dietary phosphate intake during the study period, associated with an increase in energy intake.

Median serum PTH concentrations increased at the end of the first year in those with moderate and severe CRI, and subsequently reduced back to baseline in those with moderate CRI, falling below baseline in those with severe renal failure. Analysis by UNIANOVA with the inclusion of all patients showed a highly significant increase in serum PTH concentration for the cohort as a whole, with significant differences existing

between groups. From Figure 6.5.6 (appendix 3), it is apparent that in both those with moderate and severe CRI, one child in each group exhibited a disproportionate increase in PTH over time. If these two children were excluded from the analysis, the revised UNIANOVA showed there to be no significant differences occurring over time for the cohort as a whole or for any of the three groups individually. There was an overall median reduction in plasma alkaline phosphatase over the one and two year period, although these changes were small, with the largest reduction being seen in those with severe CRI (Table 6.5.8). The changes were non-significant however for the cohort as a whole and the change observed in those with severe CRI did not reach significance when analysed by group.

Only one child with mild CRI (21) throughout the study period exhibited a serum PTH concentration that exceeded the normal range, and this returned to normal by the end of the study. No child in this group was in receipt of medication related to treatment of bone disease. Four children with moderate CRI commenced the study with serum PTH concentrations that exceeded the reference range (Table 5.3.7, appendix 2) and by the end of the study there were 9 children with above normal PTH concentrations. Three of the four children who had high baseline concentrations continued to exhibit raised concentrations (children 32, 37, 43), despite introduction of alfacalcidol in all three. Child 37 appeared to be responding to treatment, whereas child 32 was not commenced on alfacalcidol until the end of the study. There were concerns that child 43 was not compliant with medications, although a substantial reduction in phosphate intake was reported in this child. All 3 children exhibited normal plasma phosphate concentrations. Child 42 demonstrated both plasma phosphate and PTH concentrations that exceeded the normal range. There were also concerns regarding compliance, as this child had been prescribed alfacalcidol and this child also failed to provide a food diary for analysis at the end of the study. Both children (42 and 43) happened to be male adolescents. Child 35 exhibited raised plasma phosphate and PTH concentrations at one year, and was the only child with moderate CRI to be commenced on calcium carbonate. Subsequently, along with reported reductions in dietary phosphate, plasma phosphate returned to normal and serum PTH returned to just above the normal reference range, without prescription of alfacalcidol. Child 36 exhibited increased plasma phosphate and PTH concentrations and was not in receipt of medication for this. This child however, went on to receive dialysis after 1 year in the study. Of the 10

children with moderate CRI who received alfacalcidol during the study, only 4 children demonstrated a reduction in serum PTH concentration, and only 50% of those prescribed alfacalcidol, exhibited PTH concentrations within the normal range by the end of the study.

For children with severe CRI, all but one child had been in receipt of alfacalcidol and 9 children had been prescribed calcium carbonate during the study (Table 6.1.7). Ten children (53%) with severe CRI had raised PTH concentrations at baseline, and by the end of the study five (38%) children had concentrations above normal. Three of these children (57, 60, 62) exhibited high PTH concentrations throughout the study period, despite being prescribed both alfacalcidol and calcium carbonate. Their plasma phosphate concentrations however, were within the normal reference range. Child 57 demonstrated a soaring serum PTH, and this was felt to be a result of her non-compliance with medication, this child also being an adolescent. Child 49 had normal plasma concentrations of phosphate and PTH at baseline, yet developed raised concentrations for both variables during the study, despite prescription of alfacalcidol. This child was one of the few with severe CRI to report an increase in dietary phosphate during the study. Child 63 was the other to demonstrate an increase in serum PTH, albeit a modest rise. Plasma phosphate concentration remained within the normal range. The increase in PTH was despite a substantial reported reduction in dietary phosphate intake and prescription of alfacalcidol. A substantial reduction in dietary calcium was also reported, although this child was prescribed calcium carbonate later in the study.

There was no correlation between changes in dietary phosphate intake and plasma phosphate, PTH or alkaline phosphatase concentrations. When the two serum PTH concentrations above 1000 ng/l were excluded from the analysis, changes in dietary calcium intakes correlated with changes in serum PTH concentrations, predominantly in children with severe CRI, with the equation $y = -0.96x + 85$ (Figure 6.5.7). Of the 8 children with mild CRI who demonstrated an increase in PTH concentration, 5 children, reported a reduction in calcium intake, for the 9 with moderate CRI who also reported food intake, 6 reported lower calcium intakes and of the 6 with severe CRI, 4 reported a reduction in calcium intake by the end of the study.

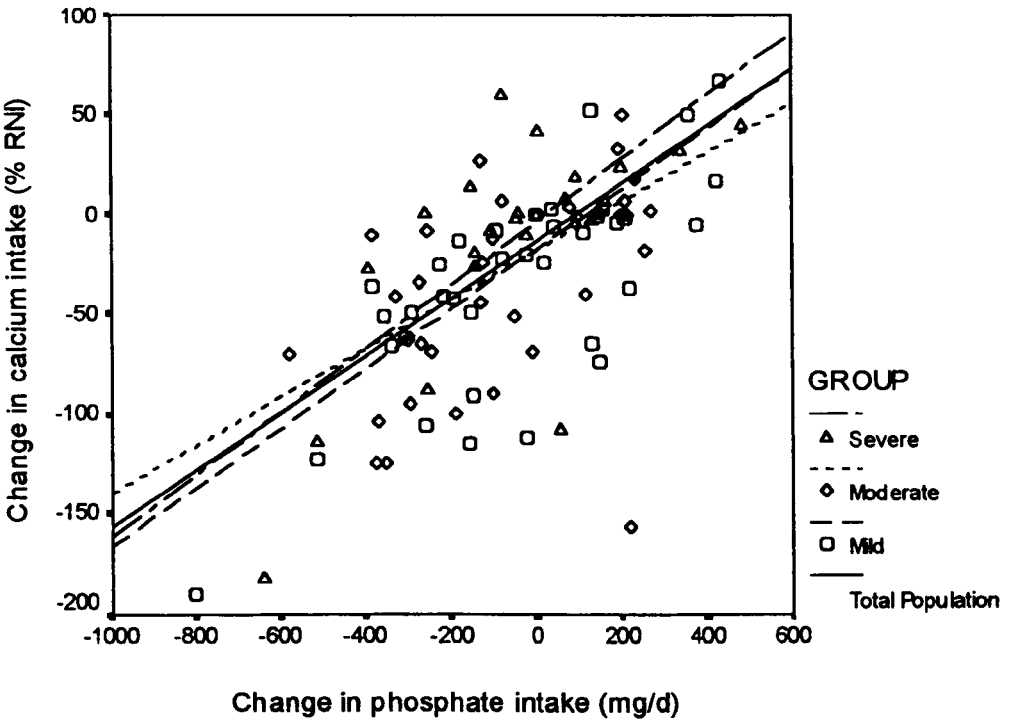
Table 6.5.4 Comparison of change in sodium, calcium and phosphate intakes (medical therapies excluded) in those who completed 1 & 2 years of the study in relation to severity of CRI

Change in nutrient Median (interquartile range)		All (N= 50; 42)*	Mild (N= 19; 16)*	Moderate (N= 18; 16)*	Severe (N= 13; 10)*
Total sodium (mmol)	Year 1	-3 (-17 – 16.5)	-1 (-15 – 32)	-11 (-22 – 9)	0 (-23 – 6)
	Year 2	10 (-13 – 29)	11 (-12 – 31)	11 (-18 – 27)	5 (-11 – 28)
Significance		[F=6.4; 1df, p=0.014]	[F=4.7; 1df, p=0.037]	[F=0.6; 1df, p=0.434]	[F=0.5; 1df, p=0.488]
Calcium (% RNI)	Year 1	-14 (-54 – 5)	-25 (-51 - -2)	-16 (-74 – 3)	1 (-23 – 19)
	Year 2	-20 (-71 - -1)	-30 (-87 - -6)	-42 (-70 - -3)	-3 (-42 – 22)
Significance		[F=33.3; 1df, p<0.001]	[F=17.9; 1df, p<0.001]	[F=11.0; 1df, p=0.002]	[F=2.21; 1df, p=0.151]
Phosphate (mg)	Year 1	-103 (-259 – 154)	-154 (-305 – 192)	-114 (-262 – 163)	6 (-149 – 129)
	Year 2	-45 (-261 – 145)	44 (-156 – 148)	-76 (-353 – 206)	-45 (-292 – 102)
Significance		[F=3.7; 1df, p=0.059][$]	[F=0.2; 1df, p=0.632]	[F=2.8; 1df, p=0.107]	[F=1.6; 1df, p=0.225]

*N= (Year 1; Year 2); RNI, reference nutrient intake

Significance is determined by UNIANOVA for changes over time, observations made at 6 monthly intervals for 2 yrs
[$]Change at end of 1 year only for all children; Visit no [F=59.01; 1df, p<0.0001]

Figure 6.5.4 Correlation between changes in calcium & phosphate intakes between groups



Total [R^2=0.43; F=33.54; 2,89df, P<0.0001]
Mild CRI [R^2=0.61; F=25.20; 2,32df, P<0.0001]
Moderate CRI [R^2=0.27; F=5.60; 2,31df, P=0.008]
Severe CRI [R^2=0.49; F=9.53; 2,20df, P=0.001]

Table 6.5.8 Comparison of changes in plasma concentrations of variables relating to bone activity in those who completed 1 & 2 years of the study in relation to severity of CRI

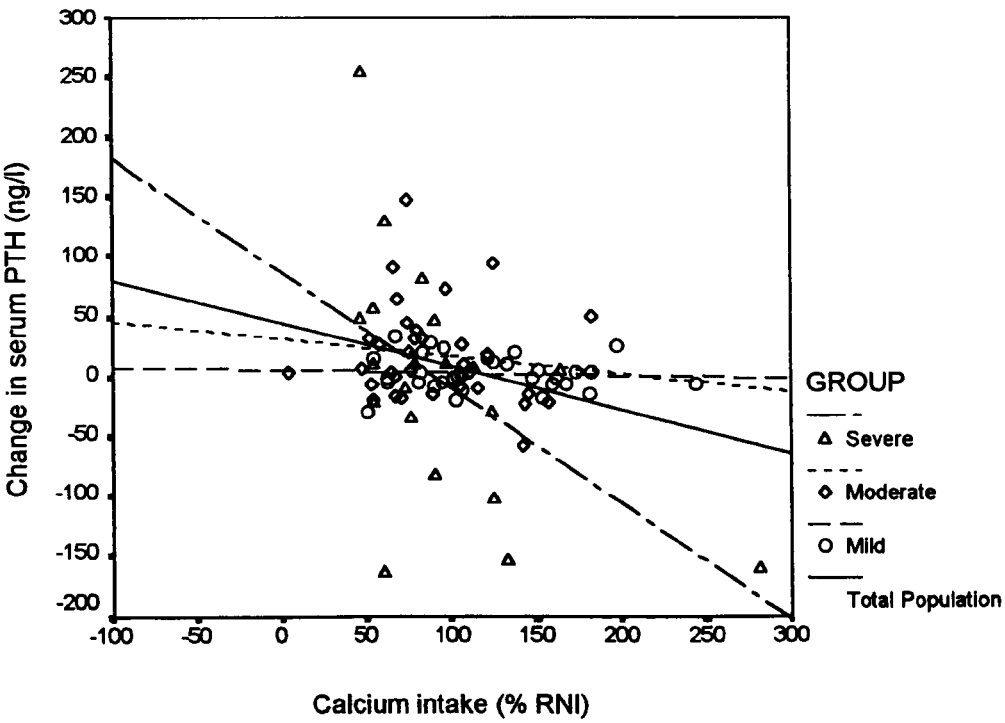
Change in variable Median (interquartile range)		All (N= 54; 50)*	Mild (N= 20; 18)*	Moderate (N= 20; 19)*	Severe (N= 14; 13)*
Calcium (mmol/l)	Year 1	-0.01 (-0.08 – 0.07)	-0.01 (-0.06 – 0.04)	-0.07 (-0.1 – 0.03)	0.1 (-0.06 – 0.22)
	Year 2	0 (-0.06 – 0.1)	-0.01 (-0.09 – 0.1)	0 (-0.05 – 0.09)	0.01 (-0.06 – 0.14)
Significance		[F=0.7; 1df, p=0.421]	[F=0; 1df, p=0.957]	[F=1; 1df, p=0.325]	[F=0.1; 1df, p=0.741]
Phosphate (mmol/l)	Year 1	0 (-0.13 – 0.12)	-0.01 (-0.13 – 0.15)	0.02 (-0.12 – 0.22)	-0.04 (-0.18– 0.08)
	Year 2	-0.05 (-0.2 – 0.09)	-0.01 (-0.12 – 0.05)	-0.13 (-0.23 – 0.04)	-0.08 (-0.26 – 0.23)
Significance		[F=1.1; 1df, p=0.297]	[F=0.1; 1df, p=0.742]	[F=3.1; 1df, p=0.081]	[F=0; 1df, p=0.972]
PTH (ng/l)	Year 1	10 (-6 – 29.8)	0 (-5 – 16)	19 (-8.8 – 48.8)	10 (-51.5 – 64.5)
	Year 2	1 (-14 – 26)	0.5 (-7.8 – 4)	1 (-10 – 38)	-10 (-86 – 53.8)
Significance		[F=19;1df, p<0.001] #	[F=0.5; 1df, p=0.481]	[F=6; 1df, p=0.021] #	[F=4; 1df, p=0.054] #
Alkaline phosphatase (mmol/l)	Year 1	-13 (-87 – 62)	10 (-69 - 70)	-21 (-91 – 176)	-72 (-177 – 46)
	Year 2	-26 (-132 – 52)	-5 (-118 - 39)	-23 (-126 - 80)	-117 (-252 – 139)
Significance		[F=1.8; 1df, p=0.179]	[F=0.1; 1df, p=0.823]	[F=0; 1df, p=0.900]	[F=2.9; 1df, p=0.092]

*N= (Year 1; Year 2)

Significance is determined by UNIANOVA for changes over time, observations made at 6 monthly intervals for 2 yrs

For PTH, exclusion of 1outlier from both moderate and severe CRI for visit no gives: All children [F=0.81; 1df, p=0.369]
Moderate CRI [F=3.74; 1df, p=0.057]
Severe CRI [F=0.03; 1df, p=0.871]

Figure 6.5.7 Correlation between calcium intake and change in serum PTH between groups



NB. 2 outliers with PTH > 1000 ng/l were excluded from the analysis

Total	[R^2=0.10; F=4.54; 2,83df, P=0.013]
Mild CRI	[R^2=0.02; F=0.36; 2,29df, P=0.701]
Moderate CRI	[R^2=0.05; F=0.75; 2,31df, P=0.482]
Severe CRI	[R^2=0.27; F=3.22; 2,17df, P=0.065]

6.6 Anaemia and iron, folate and vitamin C intakes

Changes in individual dietary iron, folate and vitamin C intakes, incorporating that provided by nutritional supplements but not micronutrient supplements, in those who completed 1 and 2 years of the study are depicted for each group of CRI in Tables 6.6.1-6.6.3 respectively (appendix 3). Fifteen children (65%) with mild CRI reported iron intakes below 100% RNI at baseline, compared with 10 children (53%) by the end of the study. Reported iron intakes fell in 8 children and increased in 10 by the end of the study. Prescription of oral iron was related to poor dietary iron intakes at baseline in all but one of the 5 children (1, 4, 6, 19, 22) with mild CRI prescribed iron during the study. Only one child (1), who reported a low dietary iron intake at baseline, but who was subsequently able to improve her intake following advice, exhibited a haemoglobin concentration below 10 g/dl at year 1, which was corrected following a course of oral iron (Table 6.6.5, appendix 3).

Eight children (35%) with mild CRI reported folate intakes below 100% RNI at baseline and by the end of the study, only 2 children (9%) reported such intakes, despite more children reporting a reduction in folate intake compared to those reporting an increase. Vitamin C intakes were also reported to be below 100% RNI in 7 children with mild CRI at baseline, which improved such that only 3 children reported suboptimal intakes by the end of the study. Children in the mild group with suboptimal intakes of folate and vitamin C did not tend to be the same children for both nutrients. Two of the 4 children (6, 24) receiving an OTC vitamin preparation at baseline reported intakes that exceeded those recommended for both folate and vitamin C throughout the study, and one child did not provide food intake data. Child 7 reported a low vitamin C intake at baseline and continued to do so during the study, although an improvement in intake was observed. The 2 children prescribed Ketovite tablets (19, 20) were not necessarily the two in greatest need of a supplement, based on reported dietary intakes, although they did report less than suboptimal intakes for one or other of the micronutrients, and were both children who had been receiving dietetic support prior to the study. The 2 children (9, 10) who reported particularly low baseline micronutrient intakes, had not been known to the dietitian before the study.

In moderate CRI, 12 children (63%) reported iron intakes below 100% RNI at baseline, compared with 14 (74%) by the end of the study. Six of the children (28, 30, 37, 39, 44,

46) at baseline reported intakes that were below 60% RNI, of which 4 were prescribed oral iron during the study period. Despite poor intakes, and possibly as a result of supplementation, no child with moderate CRI exhibited a haemoglobin concentration below 10 g/dl (Table 6.6.6, appendix 3). Reported dietary iron intakes fell in 12 children during the study, compared with an increase in 7. A total of 7 children received oral iron therapy over the course of the study. Seven children (37%) reported dietary folate intakes below 100% RNI at baseline, compared with 8 children by the end of the study. Twelve children reported a reduction in dietary folate intake during the study, whereas 7 children reported an increase. Four children reported vitamin C intakes that were below 100% RNI at baseline and at the end of the study, of which 2 children (29, 46) had exceptionally low intakes throughout. Child 29 was prescribed Ketovite tablets whereas child 46 was not, despite both of them consistently reporting low intakes of all micronutrients. A total of 7 children were prescribed Ketovite tablets, of which 5 children reported suboptimal micronutrient intakes. One child (47) was taking an OTC preparation at baseline, but subsequently stopped it, based on an adequate reported micronutrient intake.

Reported dietary iron intakes were below 100% RNI at baseline in 13 children (72%) with severe CRI, compared with 10 (76%) by the end of the study. Dietary iron intakes appeared to fall in 5 children and increase in 8 children by the end of the study period. Thirteen of the 19 children were in receipt of an oral iron preparation at some point during the study, which included 5 of the 6 children who reported dietary iron intakes below 60% RNI. The other child (60) reported low dietary intakes of all micronutrients, and despite this was not in receipt of oral iron or a vitamin supplement. This girl was a young adolescent and was in receipt of a number of medications related to hypertension and bone disease, resulting in a reluctance to prescribe further medications. She had not become anaemic, although her haemoglobin concentration dropped during the study (Table 6.6.7, appendix 3). The other 2 children to report low intakes for all micronutrients (57, 63) were both prescribed oral iron and Ketovite tablets. Reported dietary folate intakes were below 100% RNI in 10 children (56%) at baseline, compared with 6 children (46%) at the end of the study, and were suboptimal for vitamin C in 3 (17%) children at baseline compared with 4 (31%) children by the end.

Iron intake, as a % RNI, incorporating that provided by nutritional supplements but not micronutrient supplements, did not change significantly over the two year period for the cohort as a whole, or for the differing levels of severity of CRI (Table 6.6.4). There was a significant reduction in folate (% RNI) over the two year period for the cohort, with a median reduction of 7 % RNI, with no significant differences between the groups. The opposite was true for vitamin C intakes (% RNI), with a significant increase in intake being observed for the cohort as a whole, but similarly, no significant differences existing between groups. This increase appeared to predominantly occur during the second year of the study in all groups, and for the cohort as a whole, was equivalent to a median increase of 27% RNI for vitamin C during the second year. Those with moderate CRI appeared to show little change in intake over the two year period, but this was associated with a large median reduction in vitamin C intake during the first year and an equally large increase in intake during the second year.

Variables related to iron status include haemoglobin, plasma ferritin and percentage hypochromic cells. Individual values for haemoglobin concentration over the 2 year period and the changes in all 3 variables in those who completed 1 and 2 years of the study are depicted for each group of CRI in Figure 6.6 and Tables 6.6.5-6.6.7 respectively (appendix 3). A significant increase in haemoglobin concentration was observed over the 2 year period for the cohort as a whole, which was largely attributed to an increase in those with mild CRI. Fourteen children (67%) with mild CRI exhibited an increase in haemoglobin concentration over the study period, compared with 9 (50%) with moderate and 5 (39%) with severe CRI. A non-significant reduction in median haemoglobin concentration was observed in children with severe CRI, associated with an increase in the number of children with a haemoglobin of $\leq$ 10 g/dl. Of the data available, 4 (22%) children at baseline compared with 7 (54%) by the end of the study exhibited haemoglobin concentrations below 10 g/dl. Only 3 of the final 7 children had suboptimal haemoglobin concentrations at baseline (Table 5.3.23, appendix 2).

Of the children prescribed iron, all 5 children with mild CRI demonstrated an improvement in haemoglobin concentration. Of the 7 prescribed iron with moderate CRI, only 3 exhibited an improvement in haemoglobin concentration, whereas 5 had raised ferritin concentrations compared with baseline. Only one child (43) on oral iron,

who exhibited little change in plasma ferritin but showed a substantial improvement in haemoglobin, had % hypochromic cells that exceeded 10%. Two (53, 66) of the 7 children with severe CRI who were considered to have become anaemic had not been prescribed oral iron during the study. Child 53 also had raised % hypochromic cells and was of a pre-adolescent age, whereas child 66 was reaching adolescence and was in receipt of a large number of medications. Of the 5 who were anaemic that had been prescribed iron, one child (49) had also been commenced on EPO. This child demonstrated an increase in plasma ferritin and low % hypochromic cells. The other child prescribed EPO unfortunately did not have any plasma variables available to consider. Despite prescription of iron and apparent adequate ferritin stores in child 57, haemoglobin concentration reduced and % hypochromic cells increased. The developing anaemia in child 54 was associated with an increase in % hypochromic cells, despite apparent prescription of oral iron. Unfortunately there were no plasma ferritin concentrations to support this. Child 51 remained anaemic for the duration of the study, despite prescription of oral iron, ferritin concentrations above 100 μg/l and normal % hypochromic cells. Child 66 demonstrated a substantial reduction in haemoglobin concentration during the second year that was not supported by % hypochromic cells. Plasma ferritin concentrations were relatively low and this child had not been prescribed oral iron, despite falling haemoglobin concentrations.

Percentage hypochromic cells did not change significantly over time for the cohort as a whole, yet there were significant differences between groups. Those with severe CRI exhibited an increase in percentage hypochromic cells over time, which was not seen in the other groups of CRI, with three children having a value above 10%. In all 3 cases (53, 54 and 57), their haemoglobin concentration had fallen from above to below 10 g/dl. In both instances where a plasma ferritin was available however, a ferritin concentration above 100 μg/l had been achieved. Plasma ferritin significantly increased over the two year period for the cohort as a whole, but differences existed between the groups, with only those with severe CRI exhibiting a significant improvement in plasma ferritin. At the end of the two year period, 2 children with moderate (11%) and 6 children with severe CRI (50%) had plasma ferritin concentrations greater than 100 μg/l.

Table 6.6.4 Comparison of change in iron, folate and vitamin C intakes (inclusive of nutritional supplements, micronutrient supplements excluded) in those who completed 1 & 2 years of the study in relation to severity of CRI

Change in nutrient Median (interquartile range)		All (N= 50; 42)*	Mild (N= 19; 16)*	Moderate (N= 18; 16)*	Severe (N= 13; 10)*
Iron (% RNI)	Year 1	1 (-13 – 22)	5 (-8 – 31)	-7 (-16 – 24)	9 (-8 – 26)
	Year 2	4 (-35 – 21)	4 (-25 – 16)	-16 (-40 – 18)	10 (-6 – 27)
Significance		[F=0.25; 1df, p=0.617]	[F=0.18; 1df, p=0.672]	[F=0.38; 1df, p=0.541]	[F=0.32; 1df, p=0.579]
Folate (% RNI)	Year 1	-16 (-41 – 15)	-17 (-32 – 20)	-31 (-48 – 12)	-5 (-32 – 33)
	Year 2	-7 (-63 – 31)	-7 (-84 – 20)	-13 (-61 – 26)	5 (-40 – 45)
Significance		[F=5.33; 1df, p=0.024]	[F=3.31; 1df, p=0.078]	[F=1.27; 1df, p=0.267]	[F=0.18; 1df, p=0.673]
Vitamin C (% RNI)	Year 1	-3 (-72 – 56)	-1 (-71 – 99)	-20 (-111 – 45)	-6 (-33 – 80)
	Year 2	27 (-45 – 120)	12 (-53 – 126)	42 (-96 – 92)	8 (-32 – 160)
Significance		[F=4.73; 1df, p=0.034]	[F=2.75; 1df, p=0.106]	[F=0.07; 1df, p=0.790]	[F=1.76; 1df, p=0.198]

*N= (Year 1; Year 2); RNI, reference nutrient intake; suppl, nutritional supplement

Significance is determined by UNIANOVA for changes over time, observations made at 6 monthly intervals for 2 yrs

Table 6.6.8 Comparison of changes in plasma iron-related variables in those who completed 1 & 2 years of the study in relation to severity of CRI

Change in variable Median (interquartile range) {N=}		All	Mild	Moderate	Severe
Haemoglobin (g/ dl)	Year 1	0.2 (-0.4 - 0.7) {51}	0.2 (-0.3 – 1.0) {19}	0.2 (-0.6 – 1.3) {18}	0.1 (-0.4 - 0.7) {14}
	Year 2	0.5 (-0.4- 1.3) {48}	0.9 (-0.1 – 1.7) {18}	0.2 (-0.6 – 1.2) {17}	-0.3 (-1.7 – 0.7) {13}
Significance		[F=7.15; 1df, p=0.008]	[F=17.7; 1df, p<0.001]	[F=1.61; 1df, p=0.210]	[F=0.49; 1df, p=0.486]
% Hypochromic cells	Year 1	0.2 (-0.5 –1.3) {41}	0.2 (-0.7 – 0.9) {15}	0 (-0.5 – 0.2) {15}	2.2 (0.1 – 0.7) {13}
	Year 2	0.2 (-0.7 – 1.5) {38}	-0.5 (-1.9 – 0.5) {15}	0.2 (-0.1 – 2.7) {13}	1.0 (-0.2 – 8.6) {10}
Significance		[F=1.43; 1df, p=0.234]	[F=2.88; 1df, p=0.095]	[F=3.19; 1df, p=0.080]	[F=11.4; 1df, p=0.002]
Ferritin (µg/l)	Year 1	2.5 (-8.5 – 12.5) {48}	2.5 (-7.8 – 6.5) {18}	1.0 (-9.0 – 18.3) {18}	4.5 (-17.3 – 26.8) {12}
	Year 2	4.5 (-2 – 21.8) {44}	3.0 (-2.0 – 10.0) {16}	-1.0 (-7.0 – 19.5) {17}	64.0 (7.0 – 89.0) {11}
Significance		[F=5.92; 1df, p=0.016]	[F=0.15; 1df, p=0.702]	[F=1.20; 1df, p=0.277]	[F=10.4; 1df, p=0.002]

Significance is determined by UNIANOVA for changes over time, observations made at 6 monthly intervals for 2 yrs

6.7 Adherence to dietary advice

The ability of children and their families to follow the practical dietary advice given can be assessed by observing the actual change in foods eaten, as listed in the food diaries at baseline, and at one and two years later. For the majority of nutrients, a few foods for each individual tend to make up a significant proportion of intake for each nutrient. For this reason, analysis of food intake was limited to observing those foods that formed the greatest or second greatest contribution to overall intake of that nutrient, described as a proportion of total nutrient intake (%). Means of these proportions for foods that comprised the greatest and second greatest contribution were calculated, such that the values quoted in the following tables represent foods that play a prominent role in provision of specific nutrients for a group of individuals. These results can therefore be used to indicate changes in consumption of foods over time.

6.7.1 Energy

Table 6.7.1 (appendix 3) illustrates those foods that make the greatest contributions to energy intake over the two year period. Milk significantly contributed to total energy intake at baseline in more children than any other one food, being the greatest contributor to energy intake in 27% of patients, providing a mean of 17.4% of their total energy intake. Milk is restricted however, due to its high phosphate, protein and salt intake, and at the end of the two year study, it only remained the greatest contributor to energy intake in one child. The number of children with milk as the second greatest contributor to energy also reduced, as did the mean quantity of milk consumed by these individuals as a proportion of their total energy intake. Cakes and biscuits are encouraged in those children who need to increase their energy intake when they are unable to eat more starchy-based foods. Over the two year period, the proportion of children consuming substantial amounts of cakes and biscuits increased, as was seen by an increase in the number of children with these foods as the second greatest contributor to energy intake. The mean contribution to total energy intake from these foods also increased. An increase in the number of children consuming significant amounts of sugary-based drinks occurred, from 9% at baseline to 18% at the end of the two year period for the first and second greatest contributions combined, in line with advice to improve energy intake in those with poor intakes. An increase was also observed in the amount of fats and sugars added to foods and drink, but there was little change in the proportion of children that this applied to. There was a fall in the use of nutritional

supplements, in both the number of children using these products and the mean percentage of energy derived from supplements.

Fortified breakfast cereals are encouraged as they are good sources of vitamins and minerals. The total proportion of children consuming these foods however, remained constant over the two year period, as did the mean total contribution to energy intake. A similar picture occurred for bread, despite encouragement to eat more if possible. Meat and fish are encouraged as a regular part of the diet, but in moderate amounts at any one meal. Despite this, a substantial increase in the number of children with these foods as the greatest or second greatest contributor to total energy intake occurred, which reduced at two years, but did not reach baseline values. The intake of sausages and beefburgers appeared to form part of this increase. Crisps also showed a slight increase in mean contribution to energy intake and in the proportion of children consuming these foods by the second year, despite advice to limit these foods due to their salt content. Pizza was consumed by a similar number of children, but the mean contribution to energy intake fell during the two year period compared to baseline.

6.7.2 Protein

The reduction in contribution of milk to total energy intake was also born out in a reduced contribution to protein intake, with a concurrent decrease in both the number of children consuming milk and the quantity of protein provided by milk, over the two year period (Table 6.7.2, appendix 3). After baseline, one child exhibited an increase in contribution to protein intake from cheese, such that it became the greatest contributor in this child. The mean percentage contribution to protein intake from cheese otherwise fell over the two year period, in accordance with dietary advice to reduce phosphate intake. A shift to milk puddings/ yogurts occurred, from the second greatest to the greatest contributor to protein intake, in a small number of children. The greatest change in contribution to protein intake resulting from a decrease in milk was associated with an increase in the mean percentage contribution of meat and meat products. Advice would have been given to limit the intake of these foods to a small portion twice a day, but this would have taken second place to the emphasis placed on dairy products and high salt foods. For sausages and beefburgers, the pattern for protein intake was similar to that observed for energy intake, with the increase in number of children consuming substantial amounts of these products at one year returning to baseline

values after two years. A sustained increase in the mean contribution to protein intake from stews, casseroles and curry- type meals was observed for both the number of children and amount consumed. Far fewer children ate significant quantities of fish compared to meat products. Unlike the contribution towards energy intake, pizza formed a greater contribution to protein intake for more children, by the end of the two year period.

6.7.3 Sodium

As increasingly acknowledged, bread makes a substantial contribution to total sodium intake. This was apparent in this study where bread formed the greatest contribution to total sodium intake (mean of 30% of total intake), in 53% of the study population at baseline (Table 6.7.3, appendix 3). Breakfast cereals can also significantly contribute to sodium intake, but this occurred in only a small number of children. Less recognised is the contribution that milk can make to sodium intake, with a mean of 31% of total sodium intake being attributed to milk in 15% of the population at baseline, for the greatest and second greatest contributions combined. This total decreased to half the quantity, in only one patient, following advice at baseline to reduce milk intake. Crisps are eaten regularly by most children, but tend to be restricted, as they are salty snack foods that can greatly contribute to total sodium intake. In the small number of children where crisps formed the greatest contribution to salt intake, the mean contribution reduced compared to baseline. Gravies, soups and sauces are also restricted, due to being salty foods that have little nutritional value. A reduction in both the number of children and the proportional contribution to sodium intake from these foods was observed.

Manufactured products such as processed meats and tinned foods tend to contain substantial amounts of salt. The increased contribution to sodium intake from sausages and beefburgers followed the same pattern as for energy and protein intake, reflecting an increase in the number of children consuming them at one year, followed by a return to baseline intakes at the end of the study period. Baked beans and tinned spaghetti are frequently eaten by children, and although the mean percentage contribution to sodium intake from these products fell over the two year period, there was an increase in the proportion of children that this related to. An increase in the number of children where stew-type meals contributed to total sodium intake also occurred after baseline, similar

to the pattern noted for these foods towards total protein intake. The mean contribution to total sodium intake from cheese also followed a similar pattern to that noted for protein intake. Against dietetic advice, an increase in the proportion of children for which pizza formed the greatest or second greatest contribution to sodium intake occurred, accompanied by a mean increase in the combined contributions to sodium intake from pizza. The contribution from ham and bacon fluctuated over the two year period, but was a substantial contributor to sodium intake in approximately 12% of the cohort.

6.7.4 Phosphate

Dairy products, although being the predominant sources of calcium in the diet, also make substantial contributions to dietary phosphate intake and hence, have to be restricted as a means of controlling plasma phosphate concentrations in CRI. The reduction in quantity of milk consumed was associated with a reduction in the mean percentage contribution to phosphate intake from 47% at baseline, to 35% at two years, for the two greatest contributions combined (Table 6.7.4, appendix 3). The reduction in milk was accompanied by a simultaneous increase in the mean percentage contribution from milk puddings, from 12% of total phosphate intake at baseline to approximately 30% thereafter for the two greatest contributions combined. This was accompanied by a shift to a greater proportion of children exhibiting milk puddings/ yogurts as the greatest, rather than second greatest contributor to phosphate intake at two years, albeit for only a small percentage of children. The percentage contribution from cheese reduced slightly over the two year period. Eggs did not appear to form a significant part of the childrens' diets. As observed for protein and energy intakes, the contribution of meat and fish to phosphate intake increased compared to baseline, in both the proportion of children involved and the mean percentage contribution from these foods. By the end of the second year however, the proportion of children exhibiting a substantial contribution from meat/fish to phosphate intake started to fall. The contribution made predominantly by baked beans to phosphate intake reduced, such that they did not feature as either of the two greatest contributors to phosphate intake by the end of the study. The proportion of children who drank substantial quantities of cola and the mean percentage contribution to phosphate intake from cola reduced during the study, in line with dietetic advice. Although the number of children eating pizza remained constant, the percentage contribution to phosphate intake fell, whereas that for chips and potato

waffles increased after baseline. The contribution to phosphate intake from cereal products remained relatively constant during the study. The percentage contribution to phosphate intake from supplements, predominantly the complete enteral feed used in one child, dramatically reduced in the second year, due to the child being withdrawn from the study after one year.

6.7.5 Calcium

Dairy products are the major sources of calcium in the diet, and milk and cheese were noted to be the greatest contributors to calcium intake in children in this study at baseline (Table 6.7.5, appendix 3). Despite a reduction in milk intake during the study period, milk continued to be the greatest provider of calcium, as illustrated by a reduction in the mean greatest contribution from 43.9% at baseline to 32.6% at two years, in a similar proportion of children. Although the number of children consuming notable quantities of milk puddings remained constant over the two year period, a substantial increase in the mean percentage contribution to calcium intake occurred after baseline. This was associated with a shift for milk puddings/ yogurts from being the second greatest to greatest contributor to calcium intake in these children. A reduction in the number of children consuming cheese was observed in the second year, although this was accompanied by an increase in the mean percentage contribution to calcium intake. Pizza was a substantial contributor to calcium intake in approximately 20% of children at baseline, increasing to 28% of children at two years. Other milk or cheese based meals were not consumed regularly by many children, although a substantial increase in both the proportion of children and the mean percentage contribution to calcium intake occurred at one year. The percentage contribution from white and brown, flours and breads, which are fortified with calcium, exhibited an opposing pattern to that for milk-based meals. At the end of the study, bread became the second greatest contributor to calcium intake in a greater proportion of children, providing a mean of 13% of total calcium intake, apart from in two children where bread provided a mean of 35% of their total calcium intake. Baked beans were a notable source of calcium in one patient throughout the study. The mean percentage contribution to calcium intake from chocolate and chocolate products increased to 16-17% in 4-7% of children after baseline. The contribution made from nutritional supplements reduced markedly by the second year, associated with the one child who received the majority of his nutrition from a complete overnight supplement not completing the two year study.

6.7.6 Iron

The mean percentage contribution to iron from breakfast cereals remained relatively constant, but was accompanied by a greater proportion of children consuming these products, in line with recommendations to include a fortified breakfast cereal daily in the diet (Table 6.7.6, appendix 3). On the other hand, despite the mean percentage contribution of bread to iron intake remaining constant, the proportion of children that this applied to decreased after baseline. Red meat was encouraged within the portions recommended as a good source of haem iron, and accordingly, an increase in both the mean percentage contribution to iron and in the number of children that this involved was observed. A reduction in the mean percentage contribution to iron intake from baked beans was apparent, although the proportion of children that this related increased. Eggs were not a substantial contributor to iron intake during the two year study. Potato and potato products made surprisingly substantial contributions to total iron intake, in a number of children. Pizza, which was a good source of iron in three children at baseline, ceased to be so by second year. The same pattern to that for calcium and phosphate occurred, with contribution to iron intake from supplements, where the majority of total iron intake was derived from a complete enteral feed in one child.

6.7.7 Vitamin C

Few foods are responsible for substantial contributions to vitamin C intake, as illustrated in Table 6.7.7 (appendix 3), where the mean percentage contributions from foods are greater than that observed for other nutrients. Potato and potato products were the greatest contributors to vitamin C intake for the largest proportion of the cohort, with a mean percentage contribution of approximately 55% of total intake over the two year period for the greatest and second greatest contributions combined. The proportional contribution of fruit and vegetables to vitamin C intake appeared to fall during the two year period. In the first year, more children ate substantial amounts of fruit than at baseline, but unfortunately, this was not sustained during the second year. Vitamin C containing drinks such as orange juice and blackcurrant squash are encouraged as good sources of vitamin C, which formed substantial contributions to vitamin C intake for either, in approximately 25% of children. Milk surprisingly contributed to vitamin C intake in 6 children at baseline, but this declined to milk forming the greatest contribution to vitamin C in just one child by the end of the study.

6.8 Biochemical assessment (plasma proteins) of nutritional status

Although results from this section contribute towards the assessment of nutritional status in individual children, the main emphasis in this section is on the comparison of methods available, with dye binding methods being suggested to produce different plasma albumin concentrations to that determined by immunoassay (Section 2.3). The use of plasma prealbumin as a marker of nutritional status in children is also assessed.

Changes in individual markers of protein status in those who completed 1 and 2 years of the study are depicted for each group of CRI in Tables 6.8.1-6.8.3 respectively (appendix 3). One child (14) with mild CRI demonstrated a plasma albumin concentration, as determined by the dye-binding BCP method of analysis, of 35 g/l or below at baseline, compared with 4 children (13, 18, 19, 24) if measured by the ITM method. By the end of the study, 2 different children (24, 26) exhibited low albumin concentrations (BCP), both associated with an increase in proteinuria, such that the final protein: creatinine value was ≥ 0.1 g/ mmol. Changes in plasma albumin did not appear to reflect whether a child had been advised to increase or reduce energy or protein intake, or whether their height or BMI SDS had fallen or not by the BCP method of analysis. For ITM analysis of plasma albumin in children with low baseline concentrations, 2 children (13, 18) showed an improvement in albumin, with neither child exhibiting proteinuria. Child 13 reported a substantial increase in energy but not protein intake, whereas a slight reduction in both energy and protein intake was reported by the other one. One child (24) continued to exhibit values under 35 g/l associated with proteinuria and there were no follow-up measurements for the remaining child (19) with low initial baseline albumin concentrations. Two children (21, 26) developed low plasma albumin concentrations according to ITM analysis, of which one (26) was in agreement with BCP and the other was not. Child 21 did not demonstrate proteinuria. All 3 children (10, 20, 21) in the mild group who reported protein intakes within the target range (0.8-1.2g/kg) by the end of the study however, were also observed to exhibit a reduction in plasma albumin by the ITM method. This was also associated with reported reductions in energy intake, although not accompanied by reductions in BMI SDS. Child 27 developed low plasma albumin concentrations according to the ITM method only, which was not associated with proteinuria, but did coincide with a substantial reduction in reported energy and protein intake. Plasma prealbumin concentrations increased in all but 2 children with mild CRI during the study.

Seven children with moderate CRI exhibited albumin concentrations ≤ 35 g/l by the BCP method, but by the end of the study only 3 children had low concentrations, of which one was child 36, who entered the ESRD programme. Seven children were also noted to have low plasma albumin concentrations as determined by the ITM method, but in all but 2 cases (29, 38), these were in different children. By the end of the study, 5 children by the ITM method were deemed to have low plasma albumin concentrations. Child 37, one of the youngest, demonstrated an improvement in proteinuria during the study without prescription of an ACEI, but plasma albumin fell, as determined by both methods. This was only one of 2 children with moderate CRI to demonstrate a reduction in prealbumin concentration by the end of the study. Child 37 was reported to have had a significant reduction in energy intake during the study, although protein intake was reported to have increased, following cessation of nutritional supplements, due to a reduction in urinary tract infections and improved appetite and BMI SDS. Child 30 appeared to develop proteinuria, which was associated with a reduction in plasma albumin concentration by the ITM method alone, and was also associated with a reduction in reported protein intake, bringing it in line with that recommended. There was concern however, that the food diary was under-reported. Child 46 developed worsening proteinuria despite being on an ACEI and plasma albumin concentrations remained low. Growth improved in this girl, along with an increase in reported energy intake. Eight children had substantial proteinuria at baseline, compared with 11 children by the end of the study.

Six children with severe CRI commenced the study with BCP albumin concentrations ≤ 35 g/l, and by the end of the study six continued to have low values, although this was only the same children in 2 cases (60, 63). Five of the 6 children with low albumin concentrations at the end of the study also exhibited substantial proteinuria, of which 3 children were prescribed an ACEI. Six children were also considered to have low albumin concentrations by the ITM method, but this was only for the same children in 2 cases (55, 59) and as by the BCP method, all but one child exhibited substantial proteinuria. By the end of the study, 2 children by the ITM method were considered to have low plasma albumin concentrations. Only child 63 was considered to have suboptimal concentrations by both methods. This child exhibited worsening proteinuria during the study, and was in receipt of an ACEI for 18 months, but then changed to an alternative antihypertensive, due to raised plasma potassium concentrations.

Subsequently, the degree of proteinuria appeared to increase to the detriment of plasma albumin. Protein intake was also reported to have dropped, falling within the recommended intake. Child 53, who did not have substantial proteinuria, but exhibited a low plasma albumin, reported a substantial reduction in energy and protein intake, which was accompanied by a reduction in height but not BMI SDS. Twelve of the 19 children (63%) in the severe group demonstrated values for proteinuria of > 0.1 g/ mmol at baseline, compared with 50% children by the end of the study. In all children with severe CRI, prealbumin concentrations increased or remained the same compared with baseline.

Changes in plasma albumin concentration as measured by the BCP method over the 2 year period were not significant for the cohort as a whole when all children were included in the analysis (Table 6.8.4). If those with proteinuria were excluded however, an increase in plasma albumin concentration was observed for the whole cohort and for those with mild and severe CRI. A similar pattern emerged when plasma albumin was measured using the ITM assay (data for all children only shown), but a significant increase in those with severe CRI was also observed when all children including those with substantial proteinuria were included.

Correlation between plasma albumin concentrations as measured by both BCP and ITM methods were highly significant, although the correlation coefficient (R^2) was only 0.17 for the cohort as a whole, and the correlation did not appear to exist in those with severe CRI (Figure 6.8.1). If the changes in plasma albumin concentrations over the two year period were compared by correlation for the two assays, there appeared to be no relationship between the two variables for the cohort as a whole, or for any of the groups of CRI. A Bland & Altman (1986) plot to assess the discrepancy between the two assays was conducted, and showed strong agreement between the means of the two methods, but with a 2SD variation about the mean of $\pm$ 10 g/ l (Figure 6.8.2). Those with severe CRI however, showed a deviation in the mean difference between ITM and BCP measurements of plasma albumin, such that the BCP assay underestimated plasma albumin concentration by approximately 2g/ l. A highly significant correlation between the difference and average of BCP and ITM was observed for the whole group [R^2=0.21; F=32.45; 2,250df, p<0.0001], each group of CRI exhibiting a similar degree of correlation.

Plasma prealbumin concentrations significantly increased with increasing age over the two year period for all groups of CRI [R^2=0.22; F=65.87; 1,240df, p<0.0001]. Plasma prealbumin concentrations did not correlate with plasma albumin as measured by the BCP method, but there was a correlation with ITM measured plasma albumin (Figure 6.8.3). This positive correlation however, only existed in children with mild CRI, with 18% of the variation in plasma albumin being attributed to a change in plasma prealbumin, and was not apparent in those with more advanced renal disease.

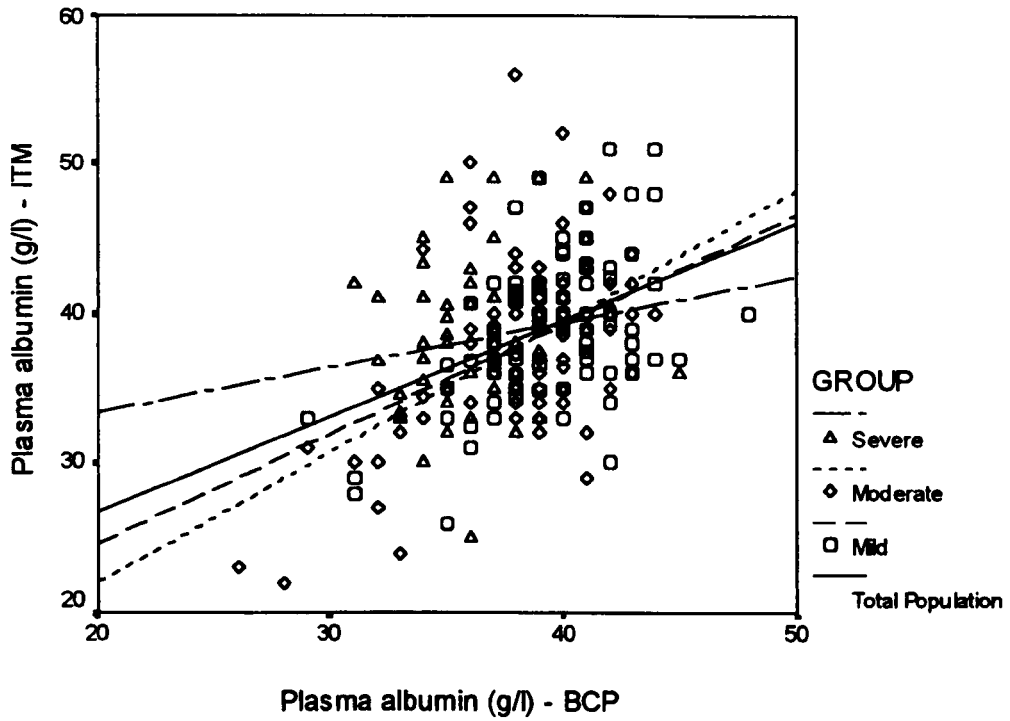
Table 6.8.4 Comparison of changes in markers of protein status in those who completed 1 & 2 years of the study in relation to severity of CRI

Change in variable Median (interquartile range) {n=}		All	Mild	Moderate	Severe
Urine protein: creatinine (g/mmol)	Year 1 Year 2	0 (0 - 0.01) {53} 0 (-0.01- 0.02) {50}	0 (0 – 0) {19} 0 (0 – 0.01) {18}	0 (0 – 0.01) {20} 0 (0 – 0.08) {19}	0 (-0.06- 0.02) {14} 0 (-0.05-0.03) {13}
Plasma albumin (g/l) BCP method [#] Significance	Year 1 Year 2	1 (-2 –3) {54} 0 (-2 – 3) {50} [F=2.1; 1df, p=0.150]	0.5 (-1 – 2) {20} 1 (-2.3 – 2.3) {18} [F=0.1; 1df, p=0.777]	1 (-2 – 3) {20} 0 (-3 – 3) {19} [F=1.5; 1df, p=0.229]	0.5 (-2 – 3) {14} 0 (-1.5 – 4.5) {13} [F=3.1; 1df, p=0.086]
Plasma albumin (g/l) [#] **if proteinuria < 0.1g/mmol** Significance	Year 1 Year 2	1 (-1 – 3) {32} 1 (-1 – 3) {30} [F=8.4; 1df, p=0.004]	1 (-1 – 2.8) {16} 1 (-0.3 – 3) {14} [F=5.2; 1df, p=0.027]	0.5 (-2.3 – 3.5) {10} 1 (-3.5 – 4.5) {9} [F=0.4; 1df, p=0.515]	1.5 (-2.5 – 3) {6} 1 (0 – 6) {7} [F=4.7; 1df, p=0.041]
Plasma albumin (g/l) ITM method Significance	Year 1 Year 2	2.1 (-3.2-4.5) {44} -0.1 (-4.2-5.2) {40} [F=3.8; 1df, p=0.052]	-0.6 (-4-2.9){17} 0 (-4.5-5.1){13} [F=0.4; 1df, p=0.556]	3.5 (-3.3-7.5){16} -0.1 (-3.6-5.8){17} [F=0.9; 1df, p=0.361]	2.5 (-2.1-7){11} 1.3 (-4.9-5.6){10} [F=4.5; 1df, p=0.039]
Plasma prealbumin (g/l) Significance	Year 1 Year 2	0.05 (0 -0.1) {47} 0.08 (0.03-0.13) {42} [F=90; 1df, p<0.001]	0.03 (0 – 0.09) {18} 0.06 (0.03- 0.11) {14} [F=54; 1 df, p<0.001]	0.06 (0.02- 0.1) {18} 0.1 (0.04- 0.14) {18} [F=41; 1df, p<0.001]	0.07 (0.02- 0.09) {11} 0.06 (0.04- 0.14) {10} [F=16; 1df, p<0.001]

[#] BCP (bromocresol purple) method; ITM, immunoturbidometric method; Proteinuria based on urine protein: creatinine ratio (g/mmol)

Significance is determined by UNIANOVA for changes over time, observations made at 6 monthly intervals for 2 yrs

Figure 6.8.1 Correlation between plasma albumin concentrations measured by the bromocresol purple (BCP) and immunoturbidometric (ITM) assays

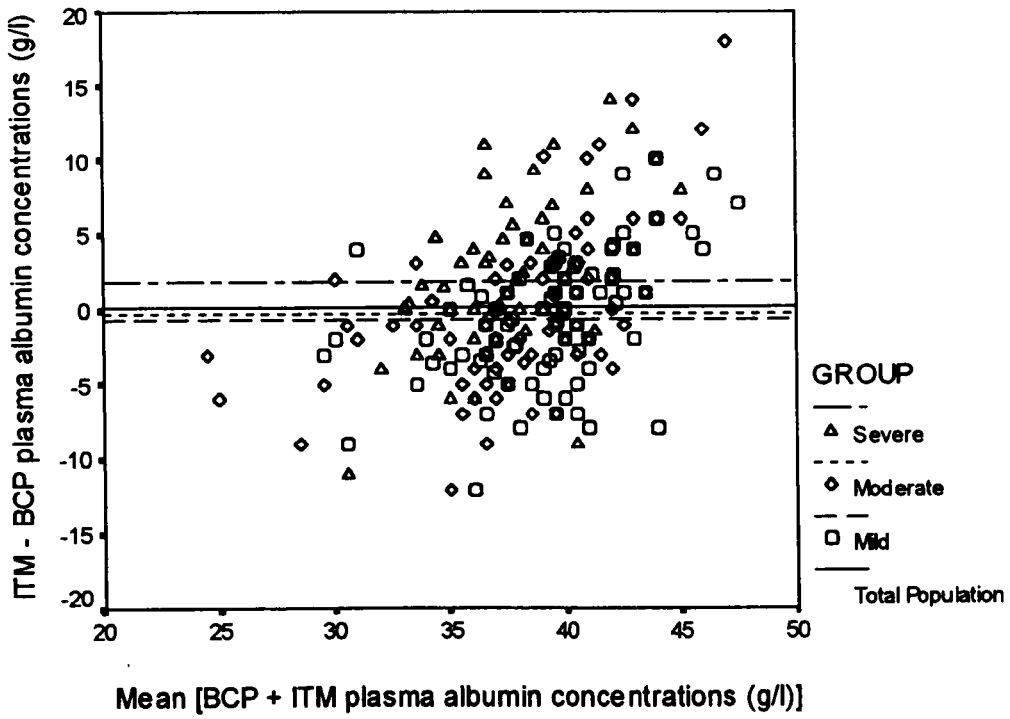


Total	[R^2=0.17; F=49.86; 1,251df, P<0.0001]
Mild CRI	[R^2=0.22; F=24.77; 1,89df, P<0.0001]
Moderate CRI	[R^2=0.25; F=29.63; 1,89df, P<0.0001]
Severe CRI	[R^2=0.03; F=2.20; 1,69df, P=0.143]

Correlation between the change in plasma albumin concentrations over the 2 year period as measured by the BCP or ITM assays:

Total	[R^2=0.03; F=2.81; 2,172df, P=0.063]
Mild CRI	[R^2=0.08; F=2.71; 2,62df, P=0.074]
Moderate CRI	[R^2=0.05; F=1.67; 2,61df, P=0.196]
Severe CRI	[R^2=0.04; F=0.77; 2,43df, P=0.470]

Figure 6.8.2 Bland & Altman plot for plasma albumin concentration as measured by the bromocresol purple (BCP) method compared to the immunoturbidometric (ITM) assay between groups

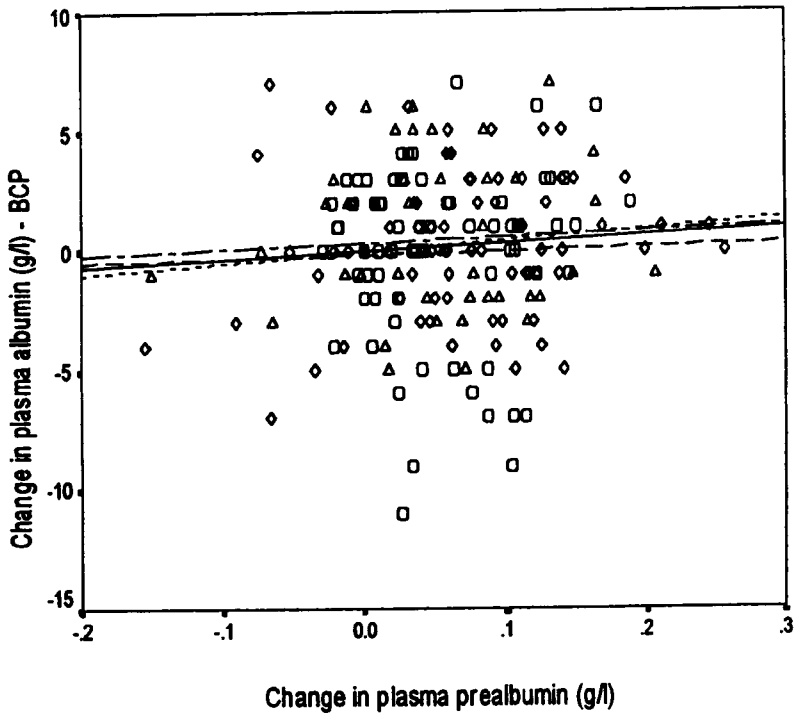


Mean (SD) for plasma albumin as measured by both methods and mean (SD) of the differences between them

Mean (SD) {n=}	Plasma albumin – BCP method	Plasma albumin – ITM method	Mean difference between methods
All	38.17 (3.3) {274}	38.38 (5.2) {253}	0.17 (4.9)
Mild CRI	39.54 (2.9) {100}	38.93 (4.7) {91}	-0.63 (4.2)
Moderate CRI	37.98 (3.5) {99}	37.84 (6.0) {91}	-0.3 (5.2)
Severe CRI	36.59 (2.6) {75}	38.37 (4.5) {71}	1.79 (4.8)

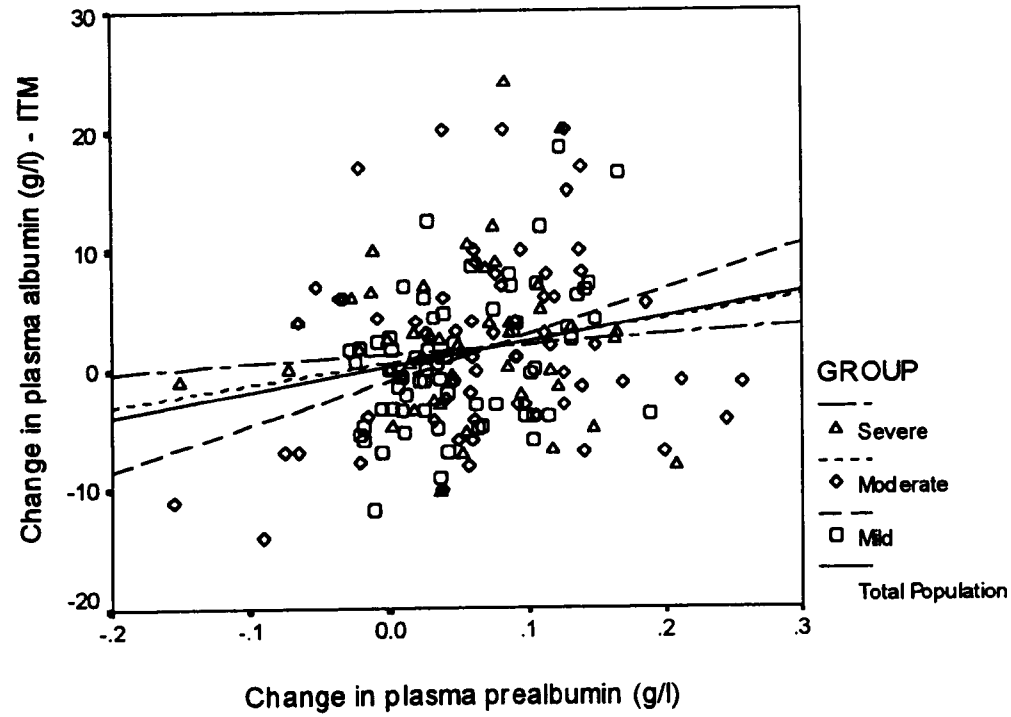
Figure 6.8.3 Correlation between changes in plasma prealbumin and albumin concentrations as measured by a) Bromocresol purple (BCP) b) Immunoturbidometric (ITM) assays

a) BCP



Total [R^2=0.01; F=0.38; 2,180df, P=0.604]
Mild CRI [R^2=0.00; F=0.05; 2,65df, P=0.955]
Moderate CRI [R^2=0.02; F=0.73; 2,66df, P=0.484]
Severe CRI [R^2=0.06; F=1.35; 2,43df, P=0.269]

b) ITM



Total [R^2=0.04; F=3.53; 2,172df, P=0.032]
Mild CRI [R^2=0.18; F=7.00; 2,62df, P=0.002]
Moderate CRI [R^2=0.03; F=1.05; 2,61df, P=0.356]
Severe CRI [R^2=0.02; F=0.38; 2,43df, P=0.688]

Chapter Seven

GENERALISED DISCUSSION

This study was designed to observe the progress of children with differing levels of CRI over a 2 year period whilst in receipt of a joint medical and dietetic package of care delivered within an established paediatric renal unit. The first aim was to compare the validity of using serum cystatin C as opposed to plasma creatinine/ height for estimation of GFR in screening for mild CRI and to compare serial measurements between cystatin C and creatinine/ height. The findings of this are discussed in chapter four, which is dedicated to this aim, the methods and statistical approaches being different to those adopted for the remaining part of the study. In summary, the indirect method of serum cystatin C appears to be as reliable as the current method used in clinical practice of estimating GFR from creatinine/ height, with the formula: height (cm) x 40/ plasma creatinine (μmol/l), in screening for CRI and for monitoring the progression of renal function. Serum cystatin C or plasma creatinine/ height estimations however, cannot replace the more invasive radioisotope or inulin clearance methods for determination of actual GFR for classification purposes. Nevertheless, results of the estimated GFR's over the 2 years were used to assess progression of CRI in all children with CRI, although conclusions regarding progression could not be validated, due to lack of serial EDTA GFR's.

The second aim was dedicated to cross-sectional comparisons for growth, dietary intakes and biochemical indices between four groups of children, those with mild, moderate and severe CRI and children denoted as having 'normal' renal function. These comparisons, which are detailed in chapter 5 also provide baseline data on each individual, with which the longitudinal changes can be compared, in the three groups of children with CRI. The data are described such that all anthropometric and blood pressure measurements, nutrient intakes and biochemical indices are reported in separate sections. Differences were noted between the groups, particularly in relation to anthropometry, hypertension, markers of bone activity and dietary adequacy of energy,

calcium and specific micronutrients. Some of the findings on a subset of the data have been published (Norman et al, 2000).

The third aim was to describe over a two year period the progress of children with differing levels of severity of CRI, in relation to their growth, nutritional intakes and biochemical status, whilst in receipt of a joint medical and dietetic package of care. The results of the longitudinal study, which address this aim are described in chapter six, along with an assessment of adherence to dietary advice, which relates to the final aim of the study. Although the majority of findings were tentative, some of the potentially most important include the suggestion that improving energy intake may improve growth in some children, attempts to reduce phosphate intake did produce a substantial reduction in calcium intake, which may cause an increase in PTH concentrations, and high sodium and phosphate intakes may be linked to progression in mild CRI. Chapter six, unlike the previous chapter of baseline data is detailed in such a way that the changes over the 2 year period are related to important clinical conditions, as discussed in sections within chapter one, the introduction. A discussion of the changes relating to each individual for all variables is also included at this point, to help explain some of the observations noted. This chapter (7), concerning the generalised discussion, addresses the issues in the same manner as chapter 6, but in the same order as chapter 1, and additionally attempts to draw the findings relating to the last three aims together. The first section of this chapter however, deals with the numerous limitations of such a clinically-based study, and the final section (7.8) refers to some of the limitations in using plasma proteins as a marker of nutritional status.

7.1 Limitations of the study and methods

The study was designed to evaluate the current joint medical and dietetic package of care employed in a specialist paediatric renal unit, describing changes observed in relation to growth, nutrition, and biochemical variables resulting from this practice over a 2 year period. There were a number of limitations associated with this:

1. Many of the children recruited to this study were known to the nephrologist, with or without dietetic input prior to the study, and consequently some children had been in receipt of medical or dietetic intervention before baseline assessment.
2. The number of children having received medical or dietetic intervention prior to recruitment was not evenly distributed across the groups, with more contacts having being made between professionals and patients in those with more severe CRI.
3. Children with severe CRI were likely to have received more regular dietetic and medical input during the study, with many children having clinic appointments every 2-3 months, compared with children with mild CRI, where 6 monthly reviews were all that was felt to be necessary.
4. The control group, referred to as the 'normal' group, may not have strictly had normal renal function, although this had not been identified by GFR. They had all been known to the renal unit previously e.g. with HUS, or had exhibited symptoms which required assessment of kidney function.
5. Due to ethical reasons involving avoiding unnecessary exposure of children to procedures, the control group was only available to provide baseline data.
6. The children were also heterogeneous in nature for underlying diagnosis and age, with children in the severe group being a mean of 2 years older than the other 2 groups of CRI, which could impact on adherence to advice and medications, and affect food choice.

For these reasons, the study could not be considered an intervention study, but it is an observational study, providing a wealth of data which is currently lacking, on the impact of a joint medical and dietetic package of care for children with CRI. As a result, relationships between nutritional intakes and biochemical variables could not be assessed to establish cause and effect, but assessment of practice could be made by

observing the progress of individuals over 2 years, in relation to their growth, biochemical variables, changes in dietary intakes and prescription of medications.

A formal assessment of GFR was only available at baseline, which was used for grouping purposes, but repeat measurements were not obtained. Changes in GFR were therefore obtained via estimation from both creatinine/ height and serum cystatin C concentrations. Limitations of these methods are discussed in detail in chapter 4. It is accepted that at present however, a gold standard is required to validate findings, and therefore conclusions could not be drawn with any confidence regarding the progression of CRI over the 2 year period.

The 6 children who failed to complete the study with mild CRI were not due to reasons associated with deteriorating renal function, whereas the 6 with severe CRI all entered the ESRD programme. The impact of this on group characteristics is discussed in section 6.1, involving baseline comparisons for age, underlying diagnosis, anthropometry, blood pressure and proteinuria between those who did and did not complete the study. The effect of differences in age in relation to food choice and how this might have changed during the 2 year period is referred to throughout the study. Food choice is affected by age, the older the child, the greater the choice they have and hence, the greater the influence they have on adopting changes to their dietary intake (Gregory et al, 2000). Food diaries were completed for cross-sectional comparison at baseline, and at yearly intervals for longitudinal comparisons. Assessment of the reliability and validity of food records is discussed in detail in section 2.1, and assessment in this study for energy intake is detailed in section 6.2.2, with comparisons made between age groups. Unfortunately, biochemical markers were not available to assess the validity of reported dietary protein and salt intakes, and hence concordance with advice can only be assumed to be similar to that found for each individual based on assessment of reported energy intake in combination with change in BMI SDS.

There was a mean difference of 2 years of age between those with mild CRI and those with severe CRI, the range being of a similar order. This difference was unlikely to have been of significance for either reliability of food intake data or food choice, with food choice being similar for an 8.5 and 10 year old. By the end of the study, the mean difference of 2.5 years was similar, but the mean age in those with mild CRI and severe

CRI was 10 and 12.5 years respectively. Children of these ages would be attending junior and senior schools respectively, with different ranges of food choice available to them. From clinical experience, it seems to be more difficult to successfully achieve adherence to dietary advice in the older group, as unfortunately many senior schools also only provide what children are seen to want, which is often chips and pizza! The influence of peer pressure is also likely to be different, with greater choice being available to the older child. The study focuses on the ability of each child to make changes to their diet over the two year period however, and does not attempt to compare differences in adherence to dietary advice between the groups. The differences in age between the groups should therefore not be a contraindication to observing the ability of a child and family to make changes to their diet, although changes in school and therefore food provision may be a factor for a few individual children in the study.

The dietetic advice provided within the study unit has remained consistent over the years, and thus patients who have been known to the study unit for a long time will have continued to receive the same advice. The way that information is presented however, has changed, with presentation of written dietary advice having improved over the last couple of years (appendix 4). This is unlikely to have had any impact on level of adherence between children who did and did not receive this particular information, as written materials have always been available. Feedback from analysis of dietary data however was delivered in different ways, depending upon whether the information was completed in time to discuss in clinic, or whether it had to be delivered via the telephone. This may have had an impact on adherence, as there is a feeling in clinical practice that more visual contact may be beneficial in improving understanding and concordance. Unfortunately, information on the children who did and did not receive visual feedback was not available, for comparisons to be drawn.

Measurement of some biochemical variables used in the study also had limitations. Children had not been fasted prior to sampling for serum lipids, and hence lipid data, particularly regarding serum triglycerides could not be considered to be reliable or valid. HDL cholesterol however, was also measured, the sampling of which is not thought to be affected by meals and hence should be valid. In addition, computerised dietary assessment of fatty acid intake was not comprehensive, with missing data being common particularly for mono-unsaturated fats. If a mono-unsaturated spread was

used, this was entered as a poly-unsaturated product, if manufacturers information was not available. This will have resulted in bias, with potential over-estimation of poly-unsaturated fat intake.

Biochemical assessment of nutritional status carries with it a number of limitations, including reliability and sensitivity of plasma albumin measurements. There are additional concerns that the most commonly used dye binding methods are unreliable in patients with more severe renal failure (section 2.3). As a result, measurement of plasma albumin was analysed by both a dye-binding and immunoturbidometric method in this study. Attempts have also been made to identify plasma markers which are more sensitive than plasma albumin for detecting deteriorating nutritional status, such as plasma prealbumin, measurements of which were also obtained. The results for both plasma albumin and prealbumin are depicted in section 6.8 and the discussion thereof now follows.

7.2 Growth, other anthropometric indices and energy intake

Growth

Linear growth is one of the most important markers of clinical outcome in the management of any child with a chronic illness. Growth impairment is a serious consequence of chronic renal failure in childhood and the psychological consequences of short stature can have a profound effect on social integration of the child. Reduced height SDS in the cross-sectional comparison of the cohort at baseline, appeared to be one of the most sensitive markers of impaired renal function. Although it has been suggested that a reduction in growth velocity occurs once the GFR has fallen below 25 ml/min/1.73m^2 (Betts & Magrath, 1974; Schaefer et al, 1996), baseline comparisons in this study would suggest that deterioration in growth starts much earlier in the course of CRI. A stepwise reduction in height SDS was observed with increasing severity of CRI, and even in those with mild CRI, a significantly lower mean height SDS was exhibited compared to that for 'normal' renal function (-0.31 vs 0.19 SDS respectively). Such early deterioration has not been previously identified, but reduction in growth in children with less severe CRI has been attributed to delayed skeletal maturation, rather than other metabolic consequences of renal disease (Hodson et al, 1983). The children in this study with 'normal' renal function may not be representative of the UK population as a whole, as the mean SDS based on the UK 90 growth reference data (Freeman et al, 1995) was greater than zero. These findings however, may reflect the continuing trend of increasing height in normal, healthy children. A recent study by Rudolf and colleagues (2000) in primary school children would appear to support this finding, with a mean height SDS for their cohort of 0.12.

The growth of those with severe CRI does reflect a 'treated' state, and thus should not strictly be compared to the growth of those who had not received intervention. It would be unethical however, to not provide appropriate intervention considering current knowledge (Chantler & Holliday, 1973; Abitbol et al, 1996; Sedman et al, 1996), and height SDS in the severe group may have been lower if energy supplementation had not been instigated prior to the study.

Mean weight SDS also decreased in a stepwise manner with increasing severity of CRI at baseline, reaching significance compared to children with 'normal' renal function in both those with moderate and severe CRI. Mean weight SDS for children with

moderate CRI in this study (–0.47) was of a similar order (-0.6) to the NAPRTCS data, whereas the mean height SDS of –0.58 compared favourably (-1.5) (Fivush et al, 1998). Mean BMI and MUAC SDS deteriorated with increasing severity, the difference across the groups becoming significant in those with severe CRI. As BMI represents weight/ height^2, an equivalent loss in weight and height will result in a reduction in BMI. MUAC merely reflects arm size relative to a child of the same age and sex, and does not compensate for the child being of small stature. MUAC may therefore appear to be suboptimal in a small child, even if the child is of correct weight for height, unless height age opposed to chronological age is used. This was not undertaken in this study however, due to a minority of children having a height SDS below –2 SDS, and the fact that this approach would not be necessary for observing change in this marker of nutritional status over time. Deterioration in growth and anthropometric parameters may have been of a greater magnitude if energy intakes had not been maintained within acceptable limits, following dietary intervention.

Over the two year period, mean height SDS significantly increased in those with severe CRI, and was maintained in both those with mild and moderate CRI, once the outlier from the mild group was excluded. Inclusion of this child, who was one of the youngest, and the only child with mild CRI to receive a nutritional supplement, resulted in a significant improvement in height SDS for this group as a whole. Mean weight SDS did not change significantly over the two year period for any of the groups of CRI, although a modest mean reduction in weight SDS was observed in children with severe CRI. This, in combination with the increase in height SDS in this group, resulted in a significant reduction in mean BMI SDS in those with severe CRI. Children with severe renal failure were older, with a mean age of 12.4 years and a greater proportion of children aged 16 years and above by the end of the study, compared with the other 2 groups of CRI. The improvement in height SDS observed in those with severe renal failure could have been a result of intensive medical and dietetic counselling, but could also have been due to catch-up pubertal growth; delayed puberty being a phenomenon commonly observed in children with renal failure (Schaefer et al, 1990). This was likely to have been the case in 3 of the children with severe CRI. The maintenance of growth in those with moderate CRI may be due to a combination of children who lost height SDS as a result of delayed pubertal growth and who gained height due to a combination of catch-up pubertal growth in at least one child and improved nutrition in

others. Maintenance of height SDS in the mild group also appeared to be associated with a combination of catch-up pubertal growth in one child and improved nutrition in another. The fact that growth was maintained during the study would suggest some benefits from intervention, as baseline comparisons suggest that growth deteriorates with worsening renal function. Renal function did appear to decline during the study, with estimations of GFR from creatinine/ height showing that approximately 45% of children with mild CRI moved into the moderate category and 30% of those with moderate CRI developed severe CRI by the end of the two year period. One third of those with severe CRI failed to complete the study due to commencement onto the ESRD programme. Unfortunately this could not be verified by a formal ^{51}CR-EDTA GFR measurement at the end of the study.

In contrast to a reduction in BMI SDS in those with severe CRI over the two year period, no change in MUAC SDS was observed over time, suggesting that nutritional status was maintained. BMI and MUAC SDS at baseline were highly correlated to each other, indicating that they are markers of the same indices i.e. that of nutritional status. If this correlation was repeated to compare the change in these variables over the two year period however, despite the correlation between BMI and MUAC SDS being highly significant, the correlation coefficient was weak. The correlation was even weaker if weight instead of BMI was compared with MUAC, suggesting that BMI is a better marker of nutritional status than weight alone. Differences between the groups of CRI in the comparison of changes in BMI and MUAC SDS over time were small, which would suggest that factors associated with discrepancies in age and pubertal status between the groups could not serve as explanatory factors for the poor correlation. It may simply be that as the SDS data derived for MUAC were only of a discreet nature, the measurements lacked sensitivity in detecting changes over time. The reference data for MUAC however, are of a cross-sectional nature and outdated, being derived from data sets of the National Health and Nutritional Examination Survey 1 of the United States, collected during 1971-1974 (Frisancho, 1974). An equivalent data set has not been developed in the UK. MUAC measurement is non-invasive, cheap, easily measured, has a high degree of reproducibility and is less affected by fluid retention than body weight. MUAC has been shown to correlate well with weight-for-height in the past (Carter, 1987), despite the cross-sectional nature of the data, but no recent work has been done to show whether MUAC SDS is appropriate 30 years on.

Percentage weight for height has proved to be an unreliable measure of nutritional status when calculated by hand from growth charts (Poustie et al, 2000). The use of BMI SDS over percentage weight for height has been recommended by the expert consensus group for use of growth reference charts in the UK (RCPCH, 2001). No guidance was provided on other anthropometric measurements. The evidence would suggest that development of reference data for MUAC SDS from a current UK population would provide an additional useful longitudinal clinical marker of nutritional status, that is independent of weight and less sensitive to changes in fluid status. In a commentary in The Lancet, Warner (2000) recommends that more direct measures of body composition such as arm anthropometry should be encompassed in the clinical assessment of a child, to permit cross-validation of weight and height data and derived indices.

Energy intakes

Voluntary energy intakes were lower with increasing severity of CRI at baseline. In patients with energy intakes less than 80% EAR, or with poor weight gain, glucose polymers and in one case a complete enteral tube feed were used. This approach was necessary in 37% of children with severe renal failure at baseline. It may potentially have had the effect of reducing the child's habitual food intake, but would not have been instigated in the first place if their appetite had been reported to be good and they were seen to be gaining weight appropriately. The proportion of children in receipt of nutritional supplements reduced over the two year period, with one child on a complete enteral feed overnight reaching end stage renal disease after one year, resulting in exclusion from the remainder of the study. The reduced usage of nutritional supplements may be associated with greater attention to detail via yearly food diary assessments, with more emphasis being placed on obtaining energy from food sources, such as added fats and sugars. In those with severe CRI however, and to a lesser extent those with moderate CRI, the median reduction in energy provided by nutritional supplements was greater than the increase in energy intake from foods alone, resulting in a non-significant decrease in energy intake over the two year period. A reduction in energy intake in this group was not the intention, and is likely to be associated with an ongoing requirement for nutritional supplements which was not being achieved by the children, due to difficulties in adhering to long term prescriptions of oral supplements.

From the validation of reported energy intake data for those with severe CRI using the EI:BMR ratio, the greatest proportion of children in the 6-18 year age category produced what could be considered to be acceptable records of energy intake throughout the two year study. The EI:BMR ratio showed a substantial reduction during the study period in children with severe CRI of 5 years of age or less, which would agree with the reduction in use of nutritional supplements over the two year period, the prescription of which were predominantly associated with this age group and would therefore not raise undue concern about inaccuracies in the reporting of other nutrients. Unfortunately, biological markers to validate the accuracy of reported intakes of other nutrients were not available, due to the absence of 24 hour urinary collections. There are some concerns however, over the use of the EI:BMR ratio for validation of reported energy intakes in children of 5 years and under in this study, as a number of children throughout were considered to be over-reporters. Despite reports in adults (Monteon et al, 1986; Schneeweiss et al, 1990) suggesting that energy requirements are not raised in CRI, findings from this study pose the question as to whether energy requirements in CRI are raised in the under five age group. This suggestion is probably unlikely however, as the proportion of over-reporters were consistent across the groups of CRI. Alternatively, it may be that estimation of BMR from the Schofield (1985) equations is not appropriate for the younger age group, the equations being based on small data sets, with under-estimation of BMR occurring. Comparison of measured BMR with calculated BMR from Schofield (1985) equations by Torun and colleagues (1996) suggest however, that calculated BMR's tend to be overestimated, although data was not available for UK children under 7 years of age. It is also worth considering whether the proposed cut-off values for children of ≤ 5 years age are realistic. It may be that the PAL values for this age group are higher than that proposed by Torun and colleagues (1996). Finally, it may be that parents of young children are keen to be seen to be providing adequate nutrition, and may therefore be over-reporting their actual energy intakes. Although parents are only asked to document what is eaten rather than what is provided, this may not have been the case in all instances.

A number of children of 6-18 years age with moderate CRI were consistently considered to be under-reporters, but as analysis predominantly focussed on change in nutrient intake, this should not have had a substantial impact upon the validity of the findings in this group. Those with mild CRI however, exhibited the greatest median

reduction in reported energy intake over the two year period, and whereas two girls in the 6-18 year age group could be considered to be under-reporters throughout the study, a substantial increase in the number of boys considered to be under-reporters occurred after baseline. This was matched by a non-significant reduction in mean BMI SDS, although the change in BMI SDS was not associated with a decrease in weight SDS, but could be attributed to a larger mean increase in height SDS over the study period. This was an intentional sequence of events for many of the children with mild CRI, with the median baseline energy intake being above average recommendations (104% EAR). Dietary advice would have been aimed at healthier eating, rather than promotion of energy intake as is frequently advised in those with severe CRI. Only two of the 6 children with mild CRI advised to reduce their energy intake however, exhibited a reduction in BMI SDS (although 2 children maintained their BMI SDS), whereas all 6 children reported reductions in energy intake. The correlation between change in weight SDS and energy intake was weak for those with mild CRI, but much stronger in those with moderate CRI, with 23% of the variation in weight SDS being attributed to a change in energy intake. Despite this, 3 of the 5 children with moderate CRI reported reductions in energy intake as advised, yet they all exhibited an increase in BMI SDS. There was therefore likely to have been an element of under-reporting, especially in those with mild CRI, and particularly in those trying to lose weight, as previously described by Schoeller (1990), although low energy reporting is not confined to overweight subjects (Livingstone et al, 1990).

Mela & Aaron (1997) attempted to gain insight into the impact of various food recording methods on the accuracy of completion by adult subjects. The respondents generally believed that they would keep honest diet records, although they were uncertain about the accuracy, particularly with semi-quantitative diaries as used by Mela and colleagues (1997) where they had to estimate portion size, this issue being pertinent to the current study. Restrained eaters and those embarrassed about their weight were more likely to generate less accurate records of their habitual food intake, even if they were of normal weight. This may be relevant to the older paediatric population, where the responsibility for reporting shifts more to the children themselves, associated with a greater degree of unstructured eating patterns and eating outside the home (Torun et al, 1996).

The effect of recording multiple food diaries on the accuracy of assessing changes in food intake over time is of concern, particularly in those with mild CRI where an increase in the number of children suggested to be under-reporting their energy intakes occurred. Concern over the validity of repeated dietary measurements in healthy adults has been highlighted by Johansson et al (1992), Kristal et al (1998) and Goris et al (2001). Validity of repeated food record data in children with CRI are not available. The GFRD study involved a comprehensive sequential assessment (baseline 4 day weighed food record and one repeated 2, 4, and 6 months after enrolment into the study) of the nutrient intake of these children (Foreman et al, 1996). Although day-to-day variation of the order of 19% was documented, similar to that observed in normal children eating an ad libitum diet (Birch et al, 1991), there was no discussion as to the validity of successive food diaries. One of the risks of bias with repeat diaries, is the recording of intakes to concur with previous expectations, known as expectation bias (Lissner et al, 1998), or response set bias (Kristal et al, 1998). A developing knowledge of their disease may also influence their reporting (exposure-suspicion bias). The fact that there was a significant reduction in energy intake over the two year period for the cohort as a whole, but not in weight or BMI SDS would suggest that an element of under-reporting does exist, particularly in the mild group, where the degree of under-reporting increased over time. If the intervention group report eating diets that match the goals of the intervention programme rather than what they actually ate, there will be a bias toward overestimating intervention effectiveness (Kristal et al, 1998). It was felt that a number of children with mild CRI were under-reporting their energy intake following advice to reduce energy intake to control weight gain, but that this was related to between meal snack foods, rather than main meals, as observed by Poppitt and colleagues in adults (1998). As a result, intake of other nutrients such as protein, phosphorus, calcium, and vitamins should be unaffected, although the possibility of this was not ruled out when interpreting the results. Kristal et al (1998) showed that even a modest dietary intervention can affect responses to dietary assessment instruments, and assessment of adherence to dietary change recommendations can be over-estimated.

One of the most remarkable findings of this study was the highly significant correlation observed over the two year period between change in energy intake and height SDS in those with severe CRI. Fifty percent of the variation in height SDS over the two year period could be attributed to a change in energy intake, a substantial observation not

reported before. From the regression line for those with severe CRI, it can be calculated that an increase in energy intake of 7% EAR was necessary to maintain growth (change in ht SDS = 0). An increase of 17% was required to promote a gain in height of 0.1 SDS. This was only observed in a small number of children however, although the numbers were comparable to those used for the regression analysis by Betts & Magrath (1974), for energy intake and growth velocity. The correlation between change in energy intake and height SDS was not significant in children with moderate CRI and did not exist in those with mild CRI. These two groups exhibited acceptable median energy intakes at the outset, with the bottom of the interquartile range being equivalent to 90-95% EAR for moderate and mild CRI respectively. An association may have been masked by the likely under-reporting observed in a number of children with both mild and moderate CRI, where reported energy intakes did not equate with change in weight and BMI SDS. In addition, increasing an already adequate intake of energy would be unlikely to affect growth, and thus a correlation between the two may not be observed.

Baseline data appeared to represent a realistic estimation of energy intake, with a median energy intake of 98% EAR in both those with moderate and mild CRI, and 94% EAR in those with severe CRI (inclusive of nutritional supplements). Foreman and colleagues (1996) on behalf of the GFRD study were not able to find an association between energy intake and severity of CRI, or height SDS. This may be due in part to the fact that they used the weighed method of dietary recording, which is known to under-report nutritional intakes (Schoeller, 1990). Foreman et al (1996) recorded a mean energy intake of only 79% of the RDA in children with mild CRI. It is therefore not surprising that they were unable to observe a difference from those with a GFR < 30 ml/min/1.73m^2. Orejas and colleagues (1995) however, noted that those children with a GFR below 50 ml/min/1.73m^2 had lower energy intakes than those with a GFR above this value. In this study, a significantly lower energy intake per kg body weight was observed at baseline in addition to the reduction in energy intake as a % EAR in children with severe CRI compared with 'normal'. This study therefore, does not support the suggestion by Foreman et al (1996) that a reduction in energy intake for chronological age is merely a consequence of a proportionally smaller body mass. In contrast, it would support the hypothesis that children with a GFR $\leq$ 50 ml/min/1.73m^2 may have lost height potential, in part associated with a reduction in energy intake.

It is suggested from these data that increasing energy intake in those with severe CRI can successfully produce catch-up growth. The fact that there was a stronger correlation between change in energy intake, rather than absolute energy intake and change in height SDS in those with severe CRI, would suggest that it may be the improvement in energy intake rather than total energy intake that is more important for promoting growth. Alternatively, it may be that, as was observed in those with moderate CRI, under-reporters of energy intake at baseline remain under-reporters throughout the study, a phenomenon also described by Black and Cole (2001). As a result, change in reported energy intake may be a more reliable and sensitive marker of change in food behaviour than reported total energy intake. In cases where the degree of under-reporting does change during the study, as observed in children with mild CRI, an association would not have been observed. Betts and Magrath (1974) showed that reduced growth velocity occurred when energy intakes fell below 80% of that recommended, and a reduction in growth velocity was only seen in children with a GFR < 25 ml/min/1.73m^2. Once energy intakes exceeded 80% RDA, no association between energy intake and statural growth could be found. It may be that if they had observed changes in energy intake with growth, they may have found an association at higher energy intakes. This hypothesis requires further validation.

The overall improvement in height SDS observed in those with severe CRI is likely to be a combination of improved nutritional intake in some children and late commencement of pubertal growth in others. Kari and colleagues (2000) have been able to demonstrate continuing catch-up growth with aggressive, ongoing nutritional support in children with a GFR < 20 ml/min/1.73m^2 over a 12 year period, without the use of growth hormone. Conversely, a recent NAPRTCS multicentre survey report (Ellis et al, 2001) concluded that height and weight SDS did not improve over one year with supplemental feeding, in children entering onto dialysis under 6 years age. This latter finding may merely reflect the fact that the study was based on a registry of data, where practices are not standardised and where variable intensity of dietetic supervision exists between the centres. With the increasing number of data registries appearing, it is vital that conclusions made in reports are treated with caution, due to the heterogeneity of such registries.

Ongoing debate exists as to whether a child with renal failure is able to follow their growth percentiles with the provision of adequate nutrition, or whether they require daily rhGH injections to prevent loss of height velocity due to growth hormone resistance. Guidelines now exist concerning the introduction of rhGH for children who have a height or height velocity for chronological age below –2 SDS (NKF-K/DOQI, 2000). They recommend that rhGH should only be administered once assurance has been made that provision of energy, protein and micronutrients is adequate and that acidosis, hyperphosphataemia and secondary hyperparathyroidism have been corrected for. Of the six children with a height below –2 SDS at baseline who completed the two year period, only two exhibited an increase in height SDS from below to above –2 SDS, both in association with a delayed pubertal growth spurt. The remaining four children, all showed an improvement in growth, albeit of not the same magnitude. Growth in the two with moderate CRI was unlikely to have been associated with puberty, whereas this was likely to have been the case in the two with severe CRI. Due to the difficulties observed in perseverance with oral nutritional supplements in those with severe CRI, and the need for additional energy of approximately 125% EAR to achieve catch-up growth (Abitbol et al, 1996), it would be appropriate to consider an enteral tube feeding route in these four children, before considering instigation of rhGH.

7.3 Hyperlipidaemia and macronutrient intake

Increasing fats and sugars are recommended in children whose appetites are suppressed, to maintain an adequate energy intake for growth. In those children where this intervention is insufficient to maintain growth and other anthropometric indices, a glucose polymer is usually currently prescribed as first line treatment. The glucose polymer powder used is maltodextrin, which is classified by the manufacturers as comprising of 89% polysaccharide, 6% sugars and 5% water. Incorporating this product into the diet of a child will appear to increase their intake of complex carbohydrate and have little effect on total sugar intake, despite this product being equivalent to increasing sugar intake from food sources. For this reason, those with severe CRI exhibited a significantly higher total carbohydrate intake (as a percentage of total energy intake) and a significantly lower sugar intake at baseline, compared to those with 'normal' renal function. Conversely, they had a significantly lower total fat intake,

as a percentage of energy, mainly as a result of a reduction in saturated fat and increase in carbohydrate intake, compared to 'normal'.

Attempts were made to replace saturated fat intake from spreads and oils with unsaturated fats such as sunflower and olive/ rapeseed oil based margarines and oils, in line with current recommendations to reduce saturated fat to below 11% of total energy intake (DoH, 1991). Specific recommendations for changes in intakes of the other major fatty acid classes, mono- and poly-unsaturated fats were not made in the UK Department of Health report (1994), due to continuing debate regarding overall benefits of additional intakes of these fatty acids. In the 1991 report (DoH, 1991), recommendations were made that poly-unsaturated fats should continue to provide an average of 6% of total energy intake and not exceed 10%, due to concerns of increased risk of tissue peroxidation in tissues containing high levels of polyunsaturated fatty acids. Mono-unsaturated fats (principally oleic acid) should continue to provide an average of 12% of dietary energy. The sum of the three types of fatty acids should equate to an average total fat intake of 35% of dietary energy. As a result of intervention having existed prior to the study, predominantly in those with severe CRI, baseline dietary fat intakes were closer to the DoH recommendations in those with more severe renal failure. A total median fat intake of 36% dietary energy, of which 15% were from saturates, was observed in children with mild CRI, whereas in those with severe renal failure, a total median fat intake of 34% of dietary energy, of which 11% were derived from saturated fats, was noted.

Use of Compeat-5 computer software for analysis of food diaries introduced an element of bias in the assessment of fatty acid intakes and other micronutrients. Manufactured foods are being produced faster than computer software is updated, and information provided by manufacturers is often limited to the macronutrient content. For fats, total fat and saturated fat are usually provided whereas the mono-unsaturated fat content is rarely given. The inputting of data is also likely to introduce errors and should be verified by a colleague. In other cases, the food has to be matched to a food with a similar composition. There are a huge range of fats and oils available, and the computer software used for this study did not distinguish between mono- and poly-unsaturated spreads. Mono-unsaturated based margarines and oils were inputted as poly-unsaturated spreads where manufacturers information was not available, and hence the

intake of poly-unsaturated spreads may be slightly overestimated and mono-unsaturates underestimated. Data from manufacturers for other products missing from the database, would often not make distinctions beyond the proportion of fats that were saturated. The sum of the three types of fatty acids therefore, did not equate to total fat intake, and it can be assumed that the difference could be predominantly attributed to mono-unsaturated fats. Cowin & Emmett (1999) however, studied the effect of missing data on calculated nutrient intakes and found the effect to be small on mean daily intakes, the underestimation being greatest for certain vitamins. Nevertheless, the effect of unsaturated fats on serum lipids in this study may not be truly represented.

All children exhibited much higher intakes of sugar as a percentage of total energy intake (median of 20-25%) than the 10% recommended (DoH, 1991), despite suggestions that patients with CRI may have a relative aversion to sucrose (Bellisle et al, 1990). Differences between the current observations and those described by Bellisle and colleagues (1990) may be due to the fact that the children in the current study were less uraemic. Reductions in sugar intake were recommended in the DoH report (1991), due to the role of non-milk extrinsic sugars in dental caries. Concern was also expressed in the report over intakes of sugar exceeding 30% of dietary energy, which could result in undesirable elevations in plasma concentrations of glucose, insulin and lipids, and could also substitute for intakes of more nutritious foods. Ludwig and colleagues (2001) suggest that energy provided in the form of sugary drinks does not compete with food intake however, thereby increasing the risk of developing childhood obesity. Conversely, encouragement of sugary drinks is therefore a useful means of increasing energy intake in children with poor appetites. Increasing sugar intakes in children however, who are already consuming 25% of their energy as sugar, may be of concern, and close attention to the frequency in consumption of sugary drinks should be made, to protect against the development of dental caries.

Changes in fat and carbohydrate intakes over the two year period differed between groups, which may be partly associated with the differences observed at baseline. Total fat intake was relatively low at baseline in those with severe CRI, and a non-significant increase was observed over the two year period, which was mostly attributed to increases in mono- and poly-unsaturated fat, in line with dietetic advice to improve energy intake. Intake of saturated fat in this group was acceptable at baseline and a

slight further reduction was observed. Those with mild and moderate CRI were able to significantly reduce their intake of saturated fat as a percentage of total energy intake over the two year period. Conversely, a significant increase in poly-unsaturated fat was observed in those with mild CRI, resulting in little change in total fat intake. On the other hand, children with moderate CRI exhibited a smaller compensatory increase in poly-unsaturated fat resulting in a non-significant reduction in total fat intake. Total carbohydrate increased, and sugar intake decreased as a percentage of total energy intake in those with mild and moderate CRI, in line with healthy eating recommendations, but the changes were not substantial enough to be considered significant. Nevertheless, only 1 child with mild CRI, who had been advised to increase sugar intake compared with 4 at baseline, reported sugar intakes that exceeded 30% of total energy by the end of the study. In those with moderate CRI, 2 children, of whom one had been advised to increase their intake, reported sugar intakes above 30% of total energy by the end of the study, compared with 5 at baseline. Conversely, a non-significant increase in sugar intake and decrease in percentage energy from total carbohydrate intake was observed in those with severe CRI, associated with a reduction in the number of children taking, and quantity consumed, of glucose polymer powder or other form of nutritional supplement during the study period. High energy drinks such as glucose based energy drinks and sugar-rich blackcurrant squashes are sometimes encouraged in these children as potentially more palatable alternatives to the proprietary prescribable energy supplements, which would have resulted in an increase in the percentage energy from sugar.

Of the 3 macronutrients, change in energy intake significantly correlated to a change in protein intake. The greatest correlation was noted in those with mild CRI, whom exhibited the greatest reduction in protein and energy intake over the two year period, with little change in percentage energy from protein. It may well be that this was one of the most successful means for reducing energy intake, in those where this was a desirable consequence, although as previously mentioned, in the majority of those children, under-reporting was suspected. It would suggest difficulties however, for children where the aim was to increase energy intake, without increasing protein intake. Protein restriction in children with CRI is often associated with a reduction in total energy intake (Berger, 1997), and Ratsch et al (1992) has demonstrated a lower spontaneous intake of energy, protein and other nutrients in children with CRI

compared with healthy children. The observation that individual reductions in plasma albumin concentrations below 35 g/l, as determined by the ITM method, seemed to be predominant in those children with mild CRI who had successfully managed to reduce their protein intake to that recommended, is of concern. It suggests that the degree of protein restriction that may be beneficial for limiting progression, may possibly be detrimental to nutritional status. Ensuring an adequate energy intake is also vital to maximise growth, and thus extreme caution should be placed on prescription of a protein restriction, without ensuring an appropriate increase in energy from other sources. From the observed increase in contribution of protein to total energy intake over the two year period in children with severe CRI, maintenance of an adequate energy intake appears to be difficult to achieve with nutritional supplements in the long term. A number of uraemic children exhibit a relative aversion for sugar (Bellisle et al, 1990), and it may be worth considering use of a concentrated liquid fat emulsion instead (4-5 kcal/ml), that can be taken as a medication 2-3 times a day, rather than the large quantities of sugary liquids usually prescribed.

The inverse relationship between change in total fat and carbohydrate intake as a percentage of dietary energy was highly significant for all groups of CRI. The strongest correlation was in those with moderate CRI, with 93% of the variation in total fat intake being attributed to a change in carbohydrate intake, suggesting that they maintained their total energy intake. This would lend further support to the suggestion that the reduction in total energy intake for the group as a whole was largely related to the reduction in protein intake. In light of this, one would have to agree with Ledermann and colleagues (1999), that describing protein as a percentage of total energy intake can be misleading in describing changes in protein intake. Reporting protein intake as both an amount per kg body weight and as a percentage of dietary energy however, would provide additionally useful information.

At baseline, only children with moderate CRI had significantly higher total cholesterol concentrations compared to 'normal'. When those with substantial proteinuria were excluded, the differences were no longer significant, and the median cholesterol was below 5 mmol/l. Children with severe CRI were the only group to exhibit a significantly raised total: HDL cholesterol concentration, compared to those with 'normal' renal function. Nevertheless, all but 3 children with severe CRI had serum

HDL cholesterol concentrations that were above 1 mmol/l at baseline. Adults who exhibit low HDL cholesterol concentration (< 1 mmol/l) and hypertriglyceridaemia (> 2 mmol/l) are reported to be at increased risk of developing cardiovascular disease (Jungers et al, 1997) and increased progression of their CRI (Samuelsson et al, 1998). Serum triglyceride concentrations were based on non-fasting samples, and hence the results were not a reliable reflection of actual blood triglyceride concentrations, the concentrations being raised following a meal. Despite this, an increasing trend in serum triglyceride concentrations with worsening severity of CRI was observed at baseline, as described by others (Querfeld, 1993; Kari et al, 1998). Although the median serum triglyceride concentration in those with severe CRI was only 1.5 mmol/l, the upper value of the interquartile range was 2.6 mmol/l, falling into the classification of hypertriglyceridaemia. Whether this was associated with the non-fasting state or not, cannot be determined.

A significant reduction in serum total cholesterol (median of 0.8 mmol/l) was observed in those with severe CRI over the two year period, which was not accompanied by a significant reduction in HDL cholesterol. The observations made for children with severe CRI were therefore related to changes in LDL cholesterol concentrations. A non-significant reduction in the total: HDL cholesterol ratio for this group resulted. Two children with severe CRI exhibited a substantial increase in HDL, accompanied by reductions in intake of glucose polymer during the study. Little change was observed in total cholesterol concentrations in the other two groups, although a significant reduction in HDL cholesterol (0.2 mmol/l) was observed in both those with mild and moderate CRI, resulting in median total HDL cholesterol concentrations however, that remained above 1 mmol/l. As a consequence, those with moderate CRI exhibited a significant increase in the total: HDL cholesterol ratio, but this did not reach significance in those with mild renal failure. In those with moderate CRI, no child had a HDL concentration below 1 mmol/l at baseline, but by the end of the study, 2 children did. It is of concern that both these children were prescribed a glucose polymer following baseline assessment, in the same way that an improvement in HDL cholesterol was associated with a reduction in glucose polymer intake in the 2 children with severe CRI. The increase in the number of children with mild CRI who had a low HDL concentration however, could not be linked to prescription of glucose polymer.

Changes in serum triglyceride concentrations were not significant during the study, and did not appear to correlate with any nutritional parameter. This may either be a true reflection of the lack of impact of dietary intervention on this variable, or more likely be due to the fact that the serum samples obtained were from non-fasted children in accordance with routine clinical practice, which does not involve measurement of serum lipids in the majority of children with milder forms of the disease.

Both sugars and complex carbohydrates have been shown to lower HDL cholesterol (Mensink & Katan, 1987) and exacerbate hypertriglyceridaemia (Grundy & Denke, 1990). It therefore follows that dietary advice should possibly be geared towards promoting fat in preference to carbohydrate in patients with CRI, low fat diets being suggested to be deleterious to cardiovascular health (Katan et al, 1997). More recent work has successfully managed to lower serum total cholesterol without lowering HDL cholesterol, via substitution of saturated fat with monounsaturated fat, rather than with carbohydrate (Williams et al, 1999). Their study diet involved an intake of 18% total energy as monounsaturated fat, 10% as saturated and 7% as polyunsaturated fat compared to 13%, 16% and 7% respectively in the control group. At the end of the study, mean total and LDL cholesterol were 0.29 and 0.38 mmol/l lower respectively, in the study group compared to controls. Hayes et al (1997) suggest that a minimum intake of 5% energy from polyunsaturated fats (namely linoleic acid) is required to counteract the hyperlipidaemic effects of the saturated fat, myristic acid.

Implications from these observations would suggest that attempts should be made to ensure that energy is increased where appropriate with the addition of unsaturated fats in preference to sugars. Consumption of additional starch does not appear to be realistic, as children did not seem to be able to increase their intake of breads, cereals and potatoes. This would add further support to the proposal that a liquid fat emulsion (currently based on refined peanut oil, high in monounsaturates) may be preferable to a glucose polymer, in improving a child's energy intake over a long period of time. Jureidini and colleagues (1990) did not show any undesirable effects on serum lipids from nutritional supplementation, and they even suggest that provision of an adequate energy intake from non-saturated sources can improve hyperlipidaemia, via improved anabolism. Hyperlipidaemia was also not shown to be exacerbated in children with chronic renal failure who were receiving enteral tube feeds (Kari et al, 1998). Improved

anabolism may partly explain the significant reduction in total cholesterol that was observed in children with severe CRI in this study, although food diary analysis showed a non-significant reduction in total energy intake and weight SDS over the two year period. Improved anabolism could be associated with more than simply an adequate energy intake however, with for example, correction of micronutrient deficiencies and metabolic acidosis, although no change in median plasma bicarbonate concentrations were observed over the two year period in those with severe CRI.

7.4 Progression of CRI

Progression of CRI in this study was determined by estimations of GFR from plasma creatinine/ height, the results and discussion surrounding the measurement and progression of CRI being described in Chapter 4. This section addresses in turn, the impact that the management of hypertension and proteinuria, and manipulation of dietary sodium, protein and phosphate intakes may have had upon the progression of CRI.

7.4.1 Hypertension and dietary sodium

A strong, independent, graded association between both systolic and diastolic blood pressure and ESRD has been reported (MRFIT, 1982; Peterson et al, 1995). DBP SDS appeared to be a determinant of whether a child had a degree of renal failure or not in this study, being significantly higher in all children with CRI compared to 'normal'. SBP SDS was less definitive, but was significantly higher in children with moderate renal failure and greatest in those with severe CRI. Goals of blood pressure therapy should be to maintain BP below the 95th percentile (< 2 SDS) for normal children of the same sex and height (de Man et al, 1991; Renal Association, 1997). At baseline, 25% of all children with CRI had a DBP greater than or equal to 2 SDS, half (53%) of which were children with severe CRI. Systolic BP was above that recommended in 32% of all children, with nearly half of the total occurring in children with severe CRI. Only 2 children with mild CRI and 3 children with moderate CRI were receiving antihypertensives at baseline, compared to approximately 50% of children with severe CRI.

Systolic blood pressure SDS significantly reduced over the two year period for the cohort as a whole (median of 0.7 SDS), and for the groups of children with mild and moderate CRI. There was no significant change in SBP SDS in those with severe CRI, probably due to the greater inter-individual variability in change in SBP SDS over the two year period. The data converted to SDS's was only of a discreet nature, which was likely to have reduced the sensitivity of the results. The mean change in DBP SDS for the cohort as a whole was half that observed for SBP SDS and unlike SBP SDS, change in DPB SDS was not significant when analysed by group. The number of children with a SBP equal to or above 2 SDS fell, from 32% at baseline to 15% at the end of the study, equally spread across the three groups. For DBP, a smaller reduction (from 25% to 19%) was noted, as observed by Wingen et al (1997), with a change in distribution between the groups, such that a reduction in the number of children with elevated DBP occurred in those with mild and severe CRI, with an increase in DBP in children with moderate CRI. Those with moderate CRI appeared to exhibit the least improvement in BP during the study period, which may reflect less aggressive medical management in this group, as suggested by the small number of children with moderate CRI receiving antihypertensives, compared to those with severe renal failure. The antihypertensive used in the majority of cases was an ACEI, as substantial proteinuria also tended to be present.

The reduction in BP SDS could not be converted to a value for actual blood pressure, due to the need to take sex and height into consideration, and hence could not be compared to published results in adults, such as the MDRD trial (Peterson et al, 1995). Wingen and colleagues (1997) however, observed a greater correlation between absolute SBP rather than height-corrected BP, and deterioration in renal function in children, with a significant difference in rate of decline associated with a cut-off SBP of < 120 mmHg. If a cut-off of 120 mmHg was used in this study, an overall reduction from 52% to 30% of the cohort with a SBP above or equal to 120 mmHg occurred over the two year period, the greatest reduction being in children with severe CRI, where a reduction by two thirds was observed.

A correlation between blood pressure and change in GFR was not apparent. Baseline comparisons between the children that did and did not complete the 2 year study however, revealed that in those with severe CRI, the children who did not complete the

study (all of which were due to reaching ESRD), exhibited almost double the mean SBP SDS compared with those remaining. Mean DBP SDS was also greater in the children with severe CRI who were unable to complete the study.

At baseline, total sodium intakes were of a similar median order of 100 mmol/d in each of the groups, although those with severe CRI had slightly higher sodium intakes. When total sodium was factored by weight, children with severe CRI however, appeared to have lower sodium intakes, of 3.5 mmol/kg compared to 4.2 mmol/kg in those with mild CRI and 'normal' renal function. Sodium intake is significantly associated with total energy intake, the latter rising with increasing age and size, and therefore it would be expected for older children to have a greater sodium intake than their younger counterparts, and would explain the higher total sodium intake in those with severe CRI. Children readily exceeded the adult recommendation of 100 mmol of sodium per day (WHO, 1999), and from the results of the latest DASH trial, it has been suggested that intakes should be reduced below this level (Sacks et al, 2001). The increased availability of lower sodium foods however, is required if this goal is to be achieved. The fact that children are consuming amounts of sodium equivalent to that recommended for adults emphasises the existing high salt intakes in children, who seem to be particularly partial to manufactured products such as crisps, sausages, pizza and baked beans.

Sodium intakes significantly increased over the two year period by a median of 10mmol/d for the group as a whole, although it was only half of that for those with severe CRI. When factored by weight, total sodium intake significantly reduced over the two year period. Nevertheless, as a large proportion of children exhibited sodium intakes in excess of the recommendation for adults at baseline, any increase in total sodium intake is undesirable, whether consuming less on a per kg basis or not. The fact that sodium intakes increased despite a reduction in energy intake is even more of a concern. When change in total sodium intake was analysed as a percentage of total energy intake, a significant increase was observed in those with mild CRI over the two year period, that was not observed in the other two groups, and was not significant for the cohort as a whole. This would suggest that those with mild CRI were less able to change their dietary habits regarding salt intake in the current climate of highly salted foods, and had actually increased their intake of salt relative to overall energy intake.

The use of a number of lower salt varieties of manufactured foods and reduced use of salt in cooking could not be accounted for, due to lack of updated computer software and unavailable nutritional information. The reported intakes of sodium derived by computer analysis of dietary diaries may subsequently be an over-representation of actual sodium intake. Although this is unlikely, an increase in the consumption of home-made stews and curries was observed over the two year period, standardised computerised recipes for which were relatively high in salt. Unfortunately, urinary sodium concentrations were not available to clarify this issue. Poor compliance to salt restriction is not an uncommon finding, with difficulties in adherence to sodium restriction being observed in adolescents (Sinaiko et al, 1993), and even in adults receiving intensive nutritional counselling with provision of low salt breads (Korhonen et al, 1999). The fact that the children were of an increasing age, may also have had an impact on food choice and concordance with dietary advice, particularly for those who had moved from primary to secondary schools, and the greater availability of food that that encompasses. The foods that continued to be consumed regularly included crisps, sausages, pizza and baked beans, which often make up secondary school meals and snacks!

Blood pressure at baseline did not correlate with sodium intake, as determined from food diary analysis. This may be a consequence of the fact that blood pressure data was only of a discreet nature. Equally, the estimation of sodium intake via food diaries is usually not a reliable marker of sodium intake. Allison & Walker (1986) compared sodium intakes of 3-5 year olds as assessed by both food diaries and urinary sodium excretion, and showed a significant correlation between the two, although the correlation was not strong ($r=0.4$), due to large individual variation. A weak correlation, of a similar order to that just described, was observed between the two measurements of sodium intake in a study assessing adherence to salt restriction in adults with mildly elevated blood pressure (Korhonen et al, 1999).

Change in sodium intake in this study however, was significantly correlated to a change in SBP but not DBP for the cohort as a whole, when sodium intake was expressed as a total per day. This relationship only existed in children with mild CRI, and it was only in this group that an association between an increase in sodium intake and deterioration in GFR was noted. In mild CRI, the majority of children who reported an increase in

dietary sodium intake exhibited an increase in SBP, and over half the children who reduced their intake were able to lower their SBP. Although there was absence of a link between total sodium intake and DBP for the cohort as a whole, a highly significant relationship existed between change in total sodium intake (mmol/kg) and DBP in children with severe CRI, with 52% of the variation in DBP being attributed to a change in sodium intake. There did appear to be a general association between individual dietary sodium intake and DBP in those with severe CRI, which did not seem to exist in the mild group. It is likely that the associations between blood pressure and sodium intake are not clear, due to the confounding effects of antihypertensives or sodium supplements in moderate and severe CRI, and due to suspicions of under-reporting, particularly in those with mild CRI.

The review by Simons-Morton and Obarzanek (1997) summarising studies on sodium intake and blood pressure in children, concluded that a higher sodium intake is related to higher blood pressure, but this could be attributed to changes in SBP, DBP or both. Reports do not appear to distinguish between differences in responses to sodium intake with varying severity of renal disease. It is suggested from these data that decreasing sodium intake in children with severe CRI has a greater effect on reducing DBP than SBP, and conversely, children with mild CRI exhibit a greater reduction in SBP than DBP. The fact that children with mild CRI exhibited greater deterioration in renal function compared to the other two groups, and that this deterioration could be associated with higher sodium intakes, would lead one to question whether a combined reduction in SBP and sodium intake is important in the prevention of progression of CRI in children with mild renal failure. True estimations of changes in SBP are difficult to determine however, due to the additional effects of 'white coat hypertension', which is particularly problematic in children (Ramsay et al, 1999). Overall, blood pressure improved over the two year period, apart from those with moderate CRI, where an increase in the number of children with a DBP equal to or greater than 2 SDS occurred, and only a 10% reduction in the proportion of children with a SBP of $\geq$ 120 mmHg was achieved.

7.4.2 Proteinuria

Proteinuria has been linked to progression of CRI (Klahr et al, 1994; Wingen et al, 1997; Ruggenenti et al, 2001) and in adults, low protein diets (0.6g/kg) have been shown to reduce proteinuria (Rosman et al, 1984; Levey et al, 1996). Frequency of proteinuria increased with worsening renal function at baseline, with 63% of children with severe CRI having proteinuria, compared to 5% in those with 'normal' function. The median urine protein: creatinine ratio did not change in any of the groups over the two year study. Renal failure however, deteriorated in approximately 80% of the children as estimated by creatinine/ height, with a estimated mean fall in GFR of 8.4 ml/min/1.73m^2 in those with mild CRI and approximately 5 ml/min/1.73m^2 in both those with moderate and severe CRI over the two year period. This degree of deterioration in the latter two groups was small, and equivalent to that described by Wingen et al (1997) for patients with congenital abnormalities. The magnitude in those with mild CRI was slightly greater than expected, particularly as this group contained the least number of children with proteinuria, which could possibly be attributed to poorer dietary compliance, although this could not be proven. Seventy to eighty percent of all children in this study had a congenital abnormality as their underlying cause of kidney disease.

Correlation between the degree of proteinuria and change in estimated GFR suggests that although small in numbers, our data are in agreement with others, that proteinuria does play a significant role in the deterioration of renal function (Klahr et al, 1994; Wingen et al, 1997). This was most apparent in those with moderate CRI, which may be due to there being a sufficient number of children with and without proteinuria for a relationship to be established. In those with severe renal failure, deterioration in GFR was significantly related to time, rather than the degree of proteinuria, the latter tending to improve with decreased functioning renal mass and use of an ACEI. Correlations at best can only suggest that a possible relationship exists between 2 variables, and there are many confounding factors that affect the validity of such findings, including prescription of an ACEI, which did not appear to be consistent across the groups. Prescription of an anti-proteinuric agent will confound establishment of an association between proteinuria and progression. Not all children with substantial proteinuria were in receipt of an ACEI, with only 4 of the 11 children (36%) with moderate CRI having been prescribed an ACEI, compared with 57% of children in the severe group. This

could explain some of the differences in correlation between those with moderate and severe CRI. Very few children with mild CRI had significant proteinuria, so that a relationship would not be apparent. Comparisons of the degree of proteinuria at baseline between children who did and did not complete the 2 year study also suggest that proteinuria is associated with deteriorating renal function. All children reaching ESRD exhibited substantial proteinuria, with a mean urine protein: creatinine ratio that was twice that of those who remained within the study.

A 50-100% increase in the use of ACE inhibitors was noted over the two year period for those with mild and moderate CRI, although this only represented about a fifth of the children in each group. The degree of proteinuria however, did not change over the two year period in any of the groups, in contrast to that observed by Maschio et al (1999) for those with mild and moderate CRI treated with an ACEI. Thirty eight percent of children with moderate CRI had a urinary protein: creatinine ratio of $\geq$ 0.1 g/ mmol, substantial proteinuria being a risk factor for progression of CRI, which can be modified by the use of an ACEI (Lazarus et al, 1997; Maschio et al, 1999). Dietary salt restriction has been shown to enhance the efficacy of ACE inhibitors in reducing proteinuria, and can contribute to delayed progression of CRI, independently from its antihypertensive effects (Heeg et al, 1989; Cianciaruso et al, 1998). The increase in DBP SDS and lack of improvement of proteinuria in those with moderate CRI would suggest under-treatment with ACE inhibitors, other antihypertensive agents and inadequate salt restriction during the study period. In children with severe CRI, the proportion of those in receipt of either a calcium channel blocker, beta blocker or ACEI remained constant over the study duration, ACE inhibitors being used in approximately 50% of the group. Such treatment was associated with an improvement in blood pressure over the two year period, but not in the degree of proteinuria. Despite this, an association between lowering of blood pressure and reduction in deterioration of renal disease was not observed in this study, unlike that found in larger studies (Klahr et al 1994; Wingen et al, 1997). Adequacy of dosage of ACE inhibitors requires evaluation in the study unit, maximal doses occasionally being contraindicated in a number of children with severe CRI, due to complications of hyperkalaemia.

Deterioration in renal function can occur for many reasons, and may also partly be explained by the fact that a number of children were entering puberty, a period of

substantial growth. Recombinant human growth hormone, or its mediator, IGF-1, has been shown to increase renal plasma flow and GFR in adults with normal renal function (Hirschberg et al, 1989), and in children with CRI (Maxwell et al, 1995). Growth hormone could therefore potentially advance the progression of CRI, in line with the hyperfiltration theory (Hostetter et al, 1981), in children with a reduced renal mass. This phenomenon is common in children who possess a congenital renal abnormality, which was the case in the majority of children in this study.

7.4.3 Dietary protein and phosphate

Total protein intake fell over the two year period by a median of 0.4 g/kg in both those with mild and moderate CRI and 0.3 g/kg in those with severe CRI, in line with dietetic advice to reduce phosphate intake, proteinuria and delay progression of the disease. The changes in median protein intake represented a significant reduction over time for both those with mild and moderate renal failure, being greatest in the former group. The true reduction in protein intake may not have been as great as that suggested however, particularly in relation to children with mild CRI, where a number were identified to be under-reporters. Those with severe CRI started with a median protein intake of 1.7 g/kg, reducing to 1.4 g/kg by the end of the study, an intake similar to that described by Foreman et al (1996). This however, should be adequate, with recommendations for healthy children in the UK being approximately 1g/ kg/ d (DoH, 1991). Advice was only of moderate protein restriction however, 'a small portion at two meals a day' plus dairy product restriction, to avoid growth impairment and the need for introduction of low protein products. Despite what was considered to be modest reductions in protein intake, all 3 children with mild CRI who reported final protein intakes within the range 0.8-1.2 g/kg, also exhibited a reduction in plasma albumin, as measured by the ITM method. This association was not so apparent in those with more severe renal failure, probably due to the presence of proteinuria.

Probably because of caution, a number of studies using 0.8-1.1g protein /kg, have failed to show beneficial effects on reducing progression of CRI in children (Kist-van Holthe tot Echten et al, 1993; Wingen et al, 1997). As might be expected, there was no correlation in this study between change in renal function and protein intake (g/ kg) over the two year period, although the decline in GFR was very small. A reduction in protein

intake of 0.4 g/kg would, according to Levey et al (1996), equate to a reduced rate of decline in GFR by 2.3 ml/min/1.73m^2 per year. The reduction in protein intake in those with mild CRI however, was likely to be overestimated. Reported protein intakes could not be validated, as 24 hour urine samples were not available for estimation of dietary protein intake from urinary nitrogen excretion. Estimation of protein intake from urea nitrogen appearance however, is confounded in children by growth, where a positive nitrogen balance is expected. Wingen et al (1993) suggest that in children with normal growth, approximately 10 mg protein/ kg/ d is required. Proteinuria increases non-urea nitrogen, which would also need to be accounted for in calculation of protein intake from UNA.

A number of studies have focused on the combined effect of reduced protein and phosphate intakes as a means of successfully reducing the progression of CRI (Walser, 1980; Maschio et al, 1982) and in the control of hyperparathyroidism (Combe et al, 1995; Martinez et al, 1997). Dietary protein restriction tends to result in a simultaneous reduction in dietary phosphate, as foods associated with high biological value protein are also high in phosphate. Surprisingly, dietary protein only weakly correlated with phosphate intake, and this was only apparent in children with moderate CRI. The greatest reductions in individual phosphate intakes appeared to be associated with substantial reductions in both dietary calcium and protein intakes in all groups of CRI. In children who reported an increase in dietary phosphate however, this was not accompanied by increases in calcium and/ or protein intakes in many cases, with a variety of changes in accompanying nutrients being observed.

In contrast to protein where no correlation was observed, dietary phosphate appeared to exhibit a non-significant inverse correlation with change in GFR, predominantly in children with mild CRI. More weight can be given to this finding by the fact that of the 8 children with mild CRI who reported final dietary phosphate intakes within the recommended limits, only 1 child exhibited deterioration in GFR of > 8 ml/min/1.73m^2, whilst 4 had changes in GFR ranging from +3 to –3 ml/min/1.73m^2. Maschio et al (1982) noted that progression was more successfully delayed in patients with mild to moderate CRI compared to those with more advanced renal failure. The differences between dietary phosphate and protein in this study could suggest that dietary phosphate restriction is more important than protein in delaying the progression of CRI in the early

stages of the disease, as recommended by Barsotti et al (1984). It may however, simply be a reflection of the concerns regarding the accuracy of reported dietary intakes, where this had less impact on misrepresentation of phosphate than protein intake. Alternatively, it may be that reduction in total dietary phosphate is more achievable than protein for affecting progression of CRI, which would hopefully have less impact on potential growth retardation. On the basis of current information and findings, attempts should be made to restrict phosphate intake as far as possible and as early in the course of CRI as possible. This is likely to produce some reduction in protein intake, but whether specific protein restriction is necessary requires further investigation, due to the potential detrimental effect of protein restriction on nutritional status (Kopple et al, 2000). Studies so far suggest that protein restriction has little benefit on delaying progression of CRI in children (Kist-van Holthe tot Echten et al, 1993; Wingen et al, 1997).

Protein intake when expressed as a percentage of total energy intake, was significantly lower in the severe group compared to the other groups at baseline. This could largely be attributed to the use of glucose polymers and low protein milk substitutes prescribed on the basis of previous dietary analyses or reported poor appetites and suboptimal weight gain. Forty percent of children with severe CRI compared to only 10% of children with moderate renal failure were in receipt of these products at baseline. A lower percentage energy from protein may be of benefit by facilitating a more positive nitrogen balance, maintaining or improving growth and reducing net urea generation (Kopple et al, 1986), which in turn may contribute to delayed progression. This may be more important than achieving an absolute reduction in protein intake commonly focused upon, when attempting to study the delay in progression (Wingen et al, 1997). Hellerstein et al (1987) recommend a diet providing 8% of the energy as protein, but in practice this is difficult to achieve. Even in those with severe CRI taking energy supplements, protein provided 11.6% of total energy intake. A non-significant increase in percentage energy from protein occurred in this group over the two year period, probably due to the reduced contribution to energy intake from energy-based nutritional supplements. Those with moderate CRI exhibited a median reduction in percentage of energy from protein to 11.8% by the second year, without the use of prescribable energy supplements. These values are in keeping with those observed by Foreman and colleagues (1996), of 12.6% total energy intake from dietary protein.

7.5 Bone metabolism, phosphorus and calcium intakes

Dietary phosphate restriction is primarily achieved via limiting dairy product intake in children, thereby reducing their intake of calcium. Baseline comparisons showed a significantly lower intake of phosphate and consequently calcium in children with severe CRI compared to 'normal', in line with instigation of dietetic advice in the majority of children with severe CRI, prior to commencement of the study. Reduction in calcium intake is undesirable, particularly as dairy product restriction resulted in a median intake of only 74% RNI in those with severe CRI at baseline, in contrast to current recommendations for healthy children and those used in the study unit of 100% RNI.

Changes in total phosphate intake were very different after one and two years, where a significant reduction for the cohort as a whole occurred in total phosphate intake at one year, but not at two years. This was associated with large reductions in dietary phosphate in children with mild and moderate CRI at one year. At the end of the study however, those with mild CRI showed a non-significant increase in phosphate intake, whereas the moderate group exhibited a smaller total reduction compared to that at one year. An increase from 53% to 74% of children who were reported to have reduced their phosphate intake to below 1000 mg/d occurred in those with moderate CRI however, compared with no improvement in those with mild CRI (50% reporting an intake below 1000 mg/d), despite the likely under-reporting in the latter group. The reduction in median intake of phosphate in children with severe CRI occurred during the second year of the study, with little change at one year. By the end of the study, 85% of children with severe CRI reported dietary phosphate intakes below 1000 mg/d, compared with 72% at baseline.

A significant reduction in calcium intake occurred for the cohort as a whole over the two year study, attributed to median reductions of 30-40% RNI in children with mild and moderate CRI by the end of the two year period. The greatest potential detrimental change to calcium intake occurred in those with moderate CRI, where 65% of the group resulted in calcium intakes below 80% RNI, and 50% of those with severe CRI also continued to exhibit calcium intakes below this level. Despite a substantial reduction in calcium intakes in children with mild CRI, only one child exhibited a calcium intake

below 80% RNI. If the aim is to achieve 100% RNI however for calcium, then intakes were reported to be below this in 42% of children with mild and 63% with moderate CRI at the end of the study, compared with 17% and 26% respectively at baseline. A slight increase in calcium was noted in those with severe CRI, where 69% of children compared with 77% at baseline reported calcium intakes below 100% RNI. Children with mild CRI would therefore overall appear to have reduced their intake of dairy products, but not to the same extent as those with moderate and severe CRI. The slight increase noted in those with severe CRI may be related to a dietetic concern that some children were reporting low calcium intakes that were not in receipt of calcium carbonate.

The variations in phosphate intake noted over the two years were not in keeping with the changes in dietary calcium, suggesting that children were able to reduce their intake of dairy products readily, but had substituted their intake of phosphate from other sources. These sources could have been related to calcium-poor protein foods such as meat, or low HBV protein or non-protein containing foods such as chips and cola. Change in dietary phosphate was nevertheless significantly correlated to a change in calcium intake, particularly in children with mild CRI, who had the highest calcium intakes at baseline. The weakest correlation was in children with moderate CRI, and it was only in this group that a correlation between change in dietary phosphate and protein intake was noted, suggesting that a greater proportion of their change in phosphate intake could be attributed to non-dairy protein sources, compared with the other groups.

A reduction in calcium intake was found to be associated with an increase in plasma PTH concentrations, predominantly in children with severe CRI. This relationship may not have been so apparent for those with moderate CRI, due to the substantial increase in prescription of alfacalcidol, associated with rising serum PTH concentrations at one year in this group. Ensuring an adequate calcium intake is important in early CRI. Amelioration of hyperparathyroidism in adults with mild CRI who were prescribed protein and phosphorus restricted diets, was only observed in those also in receipt of a calcium supplement (Martinez et al, 1997). Ratsch and colleagues (1992) described the diets of 50 Italian children with CRI who participated in the European multi-centred study (Wingen et al, 1997), and commented that deficient calcium intakes as observed

in their population are supposed to be overcome by pharmacological supplementation. There is a reluctance in clinical practice to do this however, and if dairy products are restricted in children with mild to moderate CRI at a time when other medications, phosphate binders or vitamin D preparations are not yet indicated, a calcium supplement would be indicated, which would 'medicalise' their condition. A calcium supplement however, would be a once daily medication not requiring additional medical monitoring, unlike that required for multiple phosphate binders or vitamin D therapy. Calcium carbonate was not being used in any child with mild or moderate CRI at the end of the study, rendering a substantial number of children with moderate CRI deficient in calcium.

Plasma phosphorus correlates directly with serum PTH in adults with mild to moderate CRI (Kates et al, 1997), although hyperparathyroidism in mild CRI has been shown to occur at normal serum phosphate and calcium concentrations (Martinez et al, 1997). Baseline plasma phosphate concentrations in this study support this latter observation, only becoming elevated in those with severe CRI, and even then the interquartile range fell within the normal reference range of 1.0-1.7 mmol/l. Thirty-two percent of children with severe CRI and none with moderate renal failure had been prescribed calcium carbonate prior to the study. The plasma phosphate concentrations may have been higher if the severe group had not been in receipt of medical and dietetic intervention. It may therefore be appropriate to focus initial dietetic consultations on early restriction of phosphate intake, whilst serum phosphate levels are still normal, as this may reduce hyperparathyroidism and raise serum calcitriol concentration (Brancaccio et al, 1996).

As hyperparathyroidism has been noted to develop in advance of abnormalities in serum phosphate or calcium concentrations in mild CRI, it is seen to be a more sensitive marker of abnormal bone activity (Hellerstein et al, 1987). Reichel and colleagues (1991) demonstrated a significant difference in PTH concentrations between adults with normal and mild CRI, with 32% of those in the latter group exhibiting values outside the normal reference range. Baseline intact serum PTH concentrations were significantly elevated compared to 'normal' in the study unit in both those with moderate and severe CRI. Nevertheless, the upper interquartile value for serum PTH concentration was at the upper end of the normal adult range in those with moderate CRI, and would as such possibly not warrant commencement of a vitamin D

preparation. In contrast, the interquartile range was small for those with 'normal' renal function and mild CRI, the maximum for either not extending beyond 34 ng/l.

Baseline plasma calcium concentrations in the children with CRI were not significantly different compared to 'normal', despite the use of alfacalcidol in 80% of children with severe CRI. Chan et al (1994) suggested that active forms of vitamin D should be commenced when the GFR falls below 50% of normal i.e. all those with moderate CRI should receive a vitamin D preparation. In contrast to recommendations, only 10% of children with moderate CRI were in receipt of a vitamin D analogue at baseline. Ritz and colleagues (1995) demonstrated that low-dose calcitriol (0.125μg/d) blunted the worsening of hyperparathyroidism in adults with moderate CRI without causing hypercalcaemia, hypercalciuria or hyperphosphataemia, all of which may accelerate the progression of CRI. Despite the apparent safety in administration of vitamin D analogues, there was an absence of use in children with moderate CRI in the current study. This could be associated with the fact that the adult reference range (12-72 ng/l) may be inappropriate for use in children, with the upper limit being twice that of the upper value of the interquartile range for children with 'normal' and mild CRI.

Plasma concentrations of calcium did not change significantly over the two year period, despite the increase in prescription of alfacalcidol from 10% to 50% of children with moderate CRI and up to 100% in children with severe renal failure. This increase in use of alfacalcidol is likely to be in response to an increase in serum PTH observed at one year, with median increases in PTH being noted in children with moderate and severe CRI. The increase in PTH concentration may be due to the significant reduction in dietary calcium intake, rather than due to deterioration of renal function, a correlation only being observed between the former two in children with severe CRI.

By the end of the study, the median increase in serum PTH concentration in those with moderate CRI had been rectified, although the number of children with a serum PTH that exceeded the reference range increased from 4 at baseline to 9 children at the end of the study. Of the 10 children with moderate CRI who had been prescribed alfacalcidol however, only 4 demonstrated a reduction in serum PTH. There were concerns regarding concordance with medication, which seemed to be related to age, with the greatest concerns being associated with adolescent children. A median reduction in

serum PTH was observed however, in the severe group, despite this group having an even greater number of adolescent children. It may be that treatment with alfacalcidol was more aggressive in those with severe CRI, or it could be that more children with severe CRI were prescribed calcium carbonate (9 children compared with 1 child with moderate CRI), thereby supplementing the suboptimal dietary calcium intakes. The changes in serum PTH over the two year period were non-significant, when the one extreme outlier in each of the moderate and severe group were excluded. Children with a serum PTH concentration within the 'normal' adult reference range however, were not prescribed alfacalcidol. Further research is required to determine whether the 'normal' reference range for children is equivalent to that derived for adults, to ensure intervention occurs at the earliest signs of hyperparathyroidism, in an attempt to prevent early increases in the calcium set-point for PTH inhibition (Brown et al, 1982). Changes in plasma alkaline phosphatase were also non-significant, despite a substantial median reduction in those with severe CRI, probably associated with the large inter-individual variation.

Median plasma phosphate concentrations did not significantly change over the two year period, probably due to substantial inter-individual variation. The median change in plasma phosphate concentrations however, involved a reduction in all groups, with those with moderate CRI exhibiting a median reduction of 0.13 mmol/l. The prescription of phosphate binders did not change in any of the groups during the study, suggesting that the need for instigation of calcium carbonate therapy was not apparent based on plasma phosphate concentrations. Despite deteriorating renal function, the lack of use of phosphate binders may have been partly due to the successful reduction in phosphate intake to less than 1000mg/d, in a greater proportion of children with moderate and severe CRI, by the end of the study. The indication for prescription of a phosphate binder should perhaps be based on the need for a calcium supplement, if dietary phosphate intakes have been successfully reduced, resulting in suboptimal calcium intakes.

There was a lack of correlation between the change in dietary phosphate intake and plasma markers of bone metabolism. This would be expected in children with mild CRI, due to the lack of change in their phosphate intake during the study, and in those with severe CRI, many of the children were already successfully following a phosphate

restricted diet. Those with moderate CRI were more successful in reducing dietary phosphate, but the change in intake during the study was not significant, probably due to the large inter-individual variation. Changes in plasma phosphate concentrations were not affected by prescription of phosphate binders, as this did not change over the two year period. Plasma phosphate concentrations can rise with administration of vitamin D analogues however, and there was an increase in prescription of these in both the moderate and severe groups of CRI. This could therefore have had a confounding effect on the lowering of plasma phosphate concentrations via reduction of dietary phosphate intake in these groups. The addition of alfacalcidol would also confound determination of the effects of reducing dietary phosphate on serum PTH and plasma alkaline phosphatase concentrations. Serum PTH appeared to be more sensitive to changes in dietary intake than plasma phosphate, which is in agreement with others who recommend that serum PTH is the most reliable indicator for determining the need for medical and dietetic intervention (Hellerstein et al, 1987).

7.6 Anaemia and iron, folate and vitamin C intakes

Renal anaemia, predominantly due to reduced production of erythropoietin, is a major cause of LVH, and it is becoming increasingly recognised that this starts early in the course of renal failure (GFR < 50 ml/min/1.73m^2) (Levin et al, 1999). Iron deficiency anaemia is particularly common in children (Oski, 1993; Gregory & Lowe, 2000), which may be exacerbated by CRI due to anorexia, dietary restrictions and demands of rhuEPO. At baseline, children with severe CRI exhibited a significantly lower median intake of dietary iron compared to those with 'normal' renal function, although a proportion of children within each group of CRI (20% 'normal', 30% mild, 37% moderate and 50% with severe CRI) had suboptimal iron intakes (< 80% RNI). The bottom of the interquartile range for children with moderate and severe CRI was only equivalent to an intake of approximately 50% RNI for iron, with 6 children with both moderate and severe CRI reporting iron intakes below 60% RNI. Consequently, a majority of children in both groups were prescribed oral iron. Only one child with severe CRI throughout the study however, was in receipt of rhuEPO, a prevalence lower than the 13% reported by Fivush et al (1998), but a greater proportion of children (26%) were in receipt of oral iron therapy, which could explain the discrepancy in use of rhuEPO.

Intakes of iron from dietary sources did not change significantly over the two year period for any of the children. An improvement was seen however, in children with mild CRI, where 53% reported iron intakes below 100% RNI by the end of the study, compared with 65% at baseline. An increase from 63% at baseline to 74% of children with moderate CRI reported iron intakes below 100% RNI by the end of the study. There was little change in iron intakes in children with severe CRI, with approximately 75% reporting intakes below 100% RNI. A substantial increase in the prescription of oral iron occurred, with a doubling in children with both moderate and severe CRI, and by the end of the two year period, 85% of children with severe CRI were in receipt of oral iron supplementation. A small increase in prescription of iron occurred in children with mild renal failure at one year, related to poor dietary iron intakes, but this was prescribed as a short course of iron, as is common practice for treating iron deficiency anaemia in otherwise 'normal' healthy children, with the proportion of children receiving oral iron returning to baseline by the end of the study.

Anaemia can also occur as a result of a deficiency in dietary folate or vitamin B_{12} intake. Vitamin B_{12} deficiency is uncommon if some animal protein is consumed, which was the case in the majority of children in this study. Median dietary folate intakes however, were significantly lower in children with severe CRI compared to baseline, and over 25% of children with both moderate and severe CRI had folate intakes below 80% RNI, as observed by Foreman et al (1996). Folate and vitamin B_{12} deficiency however, result in megaloblastic anaemia, denoted by an increased mean cell volume which may exceed 120 fl (Oosterhuis et al, 2000), values which were not observed during this study. Deficiencies of these vitamins have also been implicated in the development of hyperhomocysteinaemia (Hankey & Eikelboom, 1999), a condition which has a prevalence of nearly 100% in patients with ESRD and which is associated with increased mortality from cardiovascular events (Moustapha et al, 1999).

A significant reduction in dietary folate intake occurred for the cohort as a whole during the study period, with a median reduction of 7% RNI for folate, although this was not significant for any of the groups individually. The greatest reductions occurred during the first year, with a median reduction of 16% RNI, which, as for protein, may reflect a staged process of dietary education. Despite more children with mild CRI reporting a reduction rather than increase in dietary folate, by the end of the study only 9%

compared with 35% at baseline reported folate intakes below 100% RNI. As a result of an increase in the number of children with suboptimal dietary folate intakes in those with more severe renal failure, a three fold increase in the number of children with moderate renal failure being prescribed a water soluble vitamin preparation (Ketovite tablets) occurred. The proportion of children with severe CRI who were prescribed Ketovite tablets remained constant during the study, with a majority of the children taking the vitamin supplement being in receipt of it prior to the study. One to three Ketovite tablets were prescribed, depending upon the amount required to provide 100% RNI for the vitamins involved, the composition of which is described in section 6.1. There appeared to be reluctance to prescribe micronutrient supplements in at least two children with severe CRI who demonstrated low iron and vitamin intakes, due to their age (both adolescents) and the fact that they were in receipt of a large number of medications to treat hypertension and bone disease. This may have been a reasonable decision, but one feels that the information should still be given to the patient, to enable them to make an informed decision; this being an example of the concordant approach.

An adequate vitamin C intake is important to improve absorption of non-haem iron (Oski, 1993). The majority of children achieved intakes above 100% RNI for vitamin C, apart from 7 children with mild CRI, the bottom of the interquartile range being 76% RNI for this group. An awareness of this by parents may explain why a greater proportion of those with mild CRI were in receipt of an OTC vitamin preparation compared to the 'normal' group. Following evidence of changes in the adequacy of micronutrient provision via food diary assessments over the two year period, as indicated by a median increase of 12% RNI for vitamin C in the mild group and only 3 children with suboptimal intakes, fewer children with mild CRI were recommended to continue their OTC preparation. Despite an increase in dietary vitamin C intake in the other two groups, additional vitamin C was also provided by the increased prescription of Ketovite tablets to rectify the inadequate dietary folate intakes. This should not have been detrimental, as intakes of 3-4 times the RNI would be required to exceed the upper limit of that recommended (100mg/d), before increasing the risk of developing oxalosis.

Haemoglobin concentrations were significantly lower in children with severe renal failure compared to 'normal', with a median of 11.4 g/dl at baseline. This would not warrant instigation of rhuEPO, although the lower interquartile value was only 10 g/dl,

with four children (21%) having a haemoglobin concentration of less than 10 g/dl. At a concentration below 11g/dl, it would be expected for those children to have been prepared for the treatment of anaemia in accordance with published guidelines (NKF-DOQI, 1997; ERA/ EDTA, 1999).

A significant increase in the median haemoglobin concentration was observed over the two year period for the group as a whole, although this was predominantly attributed to the fact an increase in haemoglobin was observed in 67% of children with mild CRI (median of almost 1g /dl), and not in those with severe renal failure. In fact, the number of children with a haemoglobin concentration of less than 10 g/dl increased to seven (54%) in those with severe CRI. The improvement in mild CRI alone was due to the fact that all 5 children with mild CRI responded to an improved therapeutic course of oral iron, as their dietary iron intake did not change significantly over this period. In contrast, children with severe CRI did not respond to oral iron supplementation, despite a doubling in the number of children being prescribed this medication. This suggests that either the children were not able to correct their iron deficiency through oral iron, as a result of either poor absorption or non-adherence to treatment, or that a proportion of these children required rhuEPO. Administration of iv iron alone, or in combination with low dose rhuEPO has been shown to be effective in the correction of anaemia in adults with a GFR between 10-40 ml/min/1.73m^2 (Silverberg et al, 2001). There is however, reluctance in the study unit to instigate more invasive treatments such as regular injections of rhuEPO. This is despite mounting evidence to suggest that quality of life, cardiovascular morbidity and exercise capacity are all improved in patients pre-dialysis, if haemoglobin concentrations are raised above 10 g/dl (US Recombinant Human Erythropoietin Predialysis Study Group, 1991).

Plasma ferritin, a measure of iron stores and therefore determinant of absolute iron deficiency, and percentage hypochromic cells, a measure of available iron and as such a marker of functional iron deficiency, are used in combination to determine body iron status. At baseline, children with severe CRI exhibited significantly higher plasma ferritin concentrations compared to the 'normal' group. This is likely to be a reflection of the greater proportion of children being in receipt of a prescribed oral iron supplement (37% of children with severe CRI, compared to 12-14% with mild and moderate CRI, and none with 'normal' kidney function). No differences were observed

between groups for percentage hypochromic cells. A significant increase in percentage hypochromic cells however, was observed in the severe group over the study period, with 3 children developing values above 10%, indicative of functional iron deficiency. An increase in plasma ferritin concentrations was noted in the same group however, with over half of those with severe CRI having plasma ferritin concentrations above the recommended 100 μg/l (ERA/ EDTA, 1999), suggesting that their body iron stores improved over the duration. This would imply that a majority of the children were taking and absorbing at least a proportion of their prescribed iron supplement. Plasma ferritin alone is an unreliable marker of iron stores however, due to it being an acute-phase reactant and thereby becoming elevated as a result of infection, and many children with raised plasma ferritin concentrations continued to have low haemoglobin concentrations. Percentage hypochromic cells appeared to be a useful adjunct for determining improvement of renal anaemia, with all 3 children exhibiting a value above 10%, demonstrating a reduction in haemoglobin concentrations from above to below 10 g/dl. This may not have been sufficient however, to overcome the functional iron deficiency, and an improvement in haemoglobin concentrations may have occurred if an intravenous course of iron had been administered. Failing any improvement from that, instigation of rhuEPO would be indicated, particularly in those children with haemoglobin concentrations consistently below 10 g/dl, despite adequate ferritin concentrations and normal % hypochromic cells.

7.7 Adherence to dietary advice

Energy

Dietary advice was provided to all children at baseline on an individual basis to ensure an adequate energy intake to promote growth, whilst avoiding excessive weight gain and exacerbation of hyperlipidaemia. In those with severe CRI, at one year the median energy intake inclusive of supplements was equal to that at baseline, but by two years, a substantial reduction in median total energy intake occurred, despite an improvement in energy intake from foods, exclusive of supplements. A similar pattern occurred in those with moderate CRI, although a smaller proportion of children in this group were in receipt of supplements. It would seem that those children prescribed nutritional supplements were unable to adhere to their prescription over a long period, with a reduction in the percentage of children continuing to take prescribed supplements, and a

reduction in the median percentage contribution from supplements to total energy intake. This is a recognised problem in clinical practice and if accompanied by continuing weight loss, early instigation of enteral tube feeding should be considered. If weight loss is also accompanied by such symptoms as loss of growth potential, nausea and poor school attendance, earlier introduction onto the dialysis and transplant programme should be considered. In those children with poor nutritional intakes predialysis, it is usually correct to assume that their dietary intakes will continue to be poor on dialysis, and if not already present, insertion of a gastrostomy button at the same time as the dialysis catheter would be recommended, irrespective of age (Watson et al, 1998). Children who receive a proportion of their nutritional requirements via a tube feeding route tend to have better micronutrient intakes and lower plasma phosphate and urea concentrations, due to the combination of renal specific formulae and lower dietary intakes.

Fats and sugars, cakes and biscuits are actively encouraged in children with poor appetites, prior to instigation of nutritional supplements, to encourage weight gain and growth. One year into the study, more children consumed cakes and biscuits and by the second year, the quantity consumed by these children also increased. For addition of fats and sugars to food and drink, it appears that it is possible to increase the consumption of these foods in children where they already make a substantial contribution to energy intake, but it is more difficult to encourage children who are not familiar with adding fats and sugars to food, to start doing so. Changing from low energy to higher energy drinks appeared to be more feasible, with a 50% increase in children where high energy drinks formed either the greatest or second greatest contribution to total energy intake. This is of particular importance, as it has been suggested that energy containing drinks have a lower impact upon reducing food intake at subsequent meals than energy consumed in the form of solids (Ludwig et al, 2001).

Protein

The greatest change to food intake over the two year period was notably the reduction in milk intake, where only one child was observed to have milk as the greatest contributor to energy intake by the end of the study, compared to 16 children at baseline. This resulted in a median reduction of approximately 25% of the contribution made by milk to total protein and phosphate intake. Milk ceased to be an important contributor to

sodium intake in all but one child after baseline. As a result, an increase in the percentage contribution to energy, protein and phosphate intakes from meat and meat products occurred. Median total protein intake significantly reduced however, by 0.2 g/kg during the first year and again in the second year, for those with mild and moderate CRI, and by 0.3 g/kg in the second year in children with severe renal failure. This would suggest that although meat intake could have increased in the first year, the increase in contribution may merely be a reflection of a more substantial reduction in milk intake. The increase in sausages and beefburgers in the first year as a contribution to total energy, protein and sodium intakes reduced again in the second year, being replaced with more fresh meat/ fish and stew-type meals, in line with advice to restrict dietary sodium. This reflects the stepwise approach of dietary advice, targeting the most important elements first.

Sodium

Bread makes a substantial contribution to total sodium intake, but is not restricted due to its importance as a provider of energy and a number of micronutrients. Despite encouraging a greater intake of cereal-based products, little change in contribution of bread and breakfast cereals to energy intakes was observed over the two year period. This is in agreement with Nelson and Paul (DoH, 1989), demonstrating that intakes of starch tend to remain constant, whereas intakes of protein, fats and sugars can change. Crisps are eaten by a majority of children, and in 12% of the study cohort, they formed the greatest or second greatest contribution to total energy and sodium intake. It is recommended that crisps or other salty snacks are limited to 2-3 packets a week. Whilst the proportion of children consuming crisps remained relatively constant, the one child at baseline who consumed considerable amounts, was able to subsequently reduce their intake. Intakes of gravies, soups and sauces were also successfully reduced. This may be facilitated by the fact that these products, excluding soup and pot savouries, are allowed if used in reduced quantities. Median total sodium intake however, over the two year period did not change significantly. This may have been confounded in part by the increase in consumption of stew-based meals, for which computerised recipes are relatively high in salt and which may not be a true reflection of home-cooked meals, following advice to limit salt. A greater proportion of children also consumed tinned baked beans and spaghetti over the two year period, although the percentage contribution to total sodium intake reduced a little. These foods would be allowed once

or twice a week, substituting lower salt varieties where possible, although these products unfortunately were not part of the dietary computer database, and their higher salt counterparts had to be entered for analysis in many cases. Pizza is a popular food in children, but unfortunately is relatively high in both salt and phosphate, providing approximately 20% of total sodium intake in 20% of children throughout the study.

Calcium

Due the substantial reduction in milk consumption, a proportional increase in the contribution of milk puddings, ice-cream and yogurt to total phosphate and calcium intakes was observed, which was not representative of an actual increase in these foods, but probably does signify little reduction in these foods during the study. This proportional change did not apply to cheese however, and in accordance with the significant reduction in total calcium intake over the two year period, a reduction in intake of cheese after baseline can be assumed. Cheese is limited to a small portion as the main protein source at one of the two main meals, two to three times a week, and yogurts/ milk puddings are limited to two or three a week. The success in adhering to a dairy product restriction however, resulted in an unwanted reduction in calcium intake, which was highly significant over the two year period, with a median reduction of 30-40% RNI in those with mild and moderate CRI by the second year. This was not compensated for by calcium supplementation during this study, which could be detrimental in the prevention of secondary hyperparathyroidism (Martinez et al, 1997).

Phosphate

A non-significant reduction in total phosphate intake was observed, which was not unexpected for those with severe CRI, the majority (72%) of whom had already reduced their intake to below 1000 mg/d prior to the study. The change in phosphate intake was significant however for the first year compared to baseline, suggesting difficulty in adhering to phosphate restriction in the long term, particularly for those with mild CRI. The reduction in calcium intake however, was significant over the whole two year period, although only one child with mild CRI reduced their intake of dairy products to such a degree that their calcium intake fell below 80% RNI. This would suggest that the inability to achieve the recommended intake for phosphate in children with mild CRI is partly due to the need to reduce dairy products further, which may not have been actively encouraged by health professionals for this group. The discrepancy between

reduction in calcium and phosphate intakes suggests that difficulties in following a phosphate restricted diet may also be associated with excessive intakes of non-dairy sources of phosphate. Cola and other dark fizzy drinks are preserved with phosphoric acid, but unfortunately are often preferred by children. Despite this, the proportion of children, and quantities consumed declined during the study, and hence were unlikely to contribute to the discrepancy. An increase in meat and meat products may have occurred in contrast to advice at one year, although this started to fall again at two years and the correlation between dietary phosphate and protein intake was weak. A substantial increase in the percentage contribution to phosphate intake from chips and potato waffles was observed at the end of the study however, which could partly explain the lack of correlation between calcium and phosphate intakes. Chips are not discouraged in children as they are popular, and are a good source of energy and vitamin C.

Iron, folate and vitamin C

Total iron intake did not change significantly during the study, whereas there was an increase in vitamin C and decrease in folate intake. A greater proportion of children were able to incorporate breakfast cereals into their diet, and advice was given to consume them at supper time if unable to do so for breakfast. An increase in both the proportion of children eating red meat and the contribution to total iron intake from red meat also occurred, in line with advice to increase dietary intake of readily absorbable haem iron. This may have been part of the explanation as to why more stew-type meals were consumed, as many children cannot eat red meat unless served in this manner. Children were also encouraged to increase their intake of vitamin C, in an attempt to improve the absorption of non-haem iron. Potatoes were by far the greatest contributors to vitamin C intake for the largest proportion of children (55%) throughout the study. Blackcurrant squash or a vitamin C enriched squash were encouraged in children who did not like fresh orange juice to improve their intake, particularly in children who did not like fruits or vegetables. This approach may have been the reason for the increase in vitamin C intake observed, as consumption of fruits and vegetables appeared to decline during the study. The latter may be a consequence of attempts to promote energy intake, by substitution of fruit with more energy dense products, which would also explain the reduction in folate intake. Ideally, an increase in energy whilst maintaining their fruit intake is desirable, but not always possible in children with small appetites.

If children were seen more frequently than 6 monthly intervals, dietetic goals could be achieved more rapidly and reinforcement of advice with support to achieve these targets could be provided. Rosman and colleagues (1984) achieved good compliance to a protein restriction of 0.4-0.6g/kg/d, attributed to frequent visits to the dietitian, and a benefit of low protein diets on the progression of renal disease was observed. The dietitian was able to change the foods in a patient's diet depending upon their changing food preferences, and from their clinical markers such as 24 hour urinary urea excretion and biochemistry, feedback could be provided. The dietitian monitored patients' satisfaction with the diet and found it seemed to initially impair their quality of life, but the proportion of patients that felt dissatisfied fell during the study such that it was suggested that patients 'got used to the diet'. In the MDRD study, good compliance to protein restriction was achieved with monthly visits to the dietitian, although this would not be feasible in clinical practice (Dolecek et al, 1995).

Wingen et al (1997) identified that adherence to the restricted protein diet was better in children in the progressive renal failure group than those in the non-progressive group, suggesting that those families with children with deteriorating renal failure were more motivated to comply to dietary recommendations. This would support the observation that children with mild CRI appeared to comply less well to dietary advice than those with moderate and severe CRI. In this study, the reduction in protein intake in those with mild CRI was more likely to be a reflection of under-reporting, but despite this, 50% of children continued to have phosphate intakes above recommended, compared to 20-30% of children with moderate and severe CRI.

In a study on adult haemodialysis outpatients to improve adherence to treatment, contracts were developed in an individualised collaborative effort between the patient and investigator (Laidlaw et al, 1999). Mutually agreed goals and reinforcers were included and the contracts signed by the patients, in line with the principles of concordance (Dickinson et al, 1999). If the patient met the contracted goal, maintained or improved their biochemistry levels, they were awarded a sticker. Patients in the study by Laidlaw et al (1999) identified the need for health care professionals to provide positive, timely feedback regarding progress made in maintaining adherence to treatment modalities. Recommendations from the study by Laidlaw and colleagues

(1999) included ensuring that the family and significant others were included during the advice-giving sessions, education should be provided regularly and supported with a range of printed materials, medications should be simplified, the form of medication being appropriate for each individual, and that patients should be encouraged to self-medicate whilst hospitalised. If improved concordance to long-term dietary advice commencing in children with mild CRI is to be successful, these recommendations need to be consolidated into a future practical 'package of care' of guidelines for children suffering with differing levels of severity of CRI. The importance of following dietary advice should be given as much emphasis by clinicians as that of taking medications, portraying a joint medical/ dietetic collaborative approach to treatment. Dietitians will need the resources to review children's' diets on a frequent basis (3-4 monthly), if concordance to treatment is to be successful.

7.8 Biochemical assessment (plasma proteins) of nutritional status

Plasma albumin is frequently used as the biochemical marker of nutritional status in clinical practice, and is usually measured by a dye-binding method rather than an immunoassay, primarily due to costs. There are concerns in clinical practice however, associated with validity of the dye-binding method, particularly in patients with CRI (section 2.3).

Plasma albumin concentrations were significantly lower in children with both moderate and severe CRI compared to 'normal' at baseline, as measured by the BCP method. This could be attributed to the increasing presence of substantial proteinuria (urine protein: creatinine $\geq$ 0.1 g/ mmol) in children with increasing severity of CRI. Differences between the groups were not significant for children with or without proteinuria at baseline, if plasma albumin was measured using the ITM assay.

Individual reductions in plasma albumin concentrations to below 35g/l generally appeared to be associated with increases in proteinuria and vice versa. Individual changes in plasma albumin as measured by the BCP method did not appear to reflect changes in energy, protein intake or growth in any of the groups of CRI. In some children however, particularly those with mild CRI, it appeared that individual reductions in plasma albumin as determined by the ITM method, seemed to be

predominant in those children who had successfully managed to reduce their protein intake to within the recommended range. The effect of dietary protein intake on plasma albumin concentrations may be more apparent in this group of CRI, as there are fewer children with substantial proteinuria, which would disguise the association. Plasma albumin measurement is known to be affected by fluid retention, but this is not likely to be relevant in a majority of children with mild CRI, or in children with plasma albumin concentrations of 30g/l or thereabouts, as found in this study. Reported energy intakes or changes in anthropometry did not seem to be related to changes in plasma albumin. It may be that reductions in plasma albumin, if measured using a more sensitive immunoassay method, are observed prior to reductions in weight and height SDS.

An improvement in plasma albumin concentration was observed for the group as a whole in those children without substantial proteinuria (urine protein: creatinine < 0.1 g/mmol) as measured by either method, with the ITM method appearing to be more independent of the degree of proteinuria than BCP. The improvement was predominantly observed in children with severe CRI, with a median increase in plasma albumin of 3 g/l in those without proteinuria, as determined by ITM, although this was only a small number of children. Those with moderate CRI with or without proteinuria demonstrated a substantial increase in plasma albumin in the first year as measured by ITM, which returned to baseline concentrations by the end of the study. The degree of change determined by the BCP method was of a much smaller magnitude for all children and would suggest that the antibody method of analysis is a more sensitive marker than the BCP dye-binding method.

In contrast to the recent study by Carfray et al (2000) comparing ITM with BCG and BCP methods in haemodialysis patients, the correlation between ITM and BCP was relatively weak, with only 17% of the variation in ITM being explained by BCP (Figure 6.8.1). The BCP method demonstrated positive bias for albumin of a similar order to that described by Carfray and colleagues (2000) for those with severe CRI, which was not observed in children with milder degrees of renal failure. The findings suggest that the BCP method underestimates plasma albumin by an average of approximately 2 g/l, this discrepancy being attributed to the binding of uraemic toxins to albumin, preventing the binding of other substances such as dyes. The effects of proteinuria on these results could not be evaluated, due to the majority of patients with severe CRI having

proteinuria. The Bland and Altman plot (1986) however, as illustrated in Figure 6.8.2, revealed a positive correlation between the difference between ITM and BCP and the mean of the two assays, which was not observed by Carfray and colleagues for BCP, but did exist for BCG. The degree of this association varied little with severity of CRI, suggesting that interference by unknown toxins in uraemic plasma is not the full explanation, although it is not apparent as to why these two methods appear to be measuring different substances. On the basis of the study by Carfrey and colleagues (2000), recommendations in the UK Renal Registry Report (2000) suggest that the BCP assay should be used in preference to BCG. Although this study cannot refute that BCP is a more valid measure of plasma albumin than BCG, the latter not having been measured, it nevertheless suggests that caution should be demonstrated in the interpretation of plasma albumin as determined by the BCP method. An antibody-based method would be the ideal solution, but this method is more expensive and therefore unlikely to be routinely adopted.

Plasma prealbumin has been recommended as an earlier marker of nutritional status than plasma albumin due to its shorter half life and the fact that it responds acutely to energy or protein intakes (Ingenbleek et al, 1994). At baseline, plasma prealbumin concentrations were significantly higher in children with moderate and severe CRI compared to 'normal'. The concentrations however, only exceeded 30 mg/dl in a small number of children, which suggests that the cut-off recommended for detecting malnutrition in adults (Sreedhara et al, 1996; NKF-K/DOQI, 2000), is not appropriate for children. Prealbumin concentrations increased with worsening renal function as expected, due to the fact that the prealbumin-RBP complex is degraded by the kidneys (Cano et al, 1988). The concentrations also significantly increased with age at baseline, although the level of agreement between the two was weak. The relationship between plasma prealbumin concentrations and age became more apparent when observing the change in these variables over the two year period, where approximately 25% of the increase in prealbumin concentration over the two year period could be attributed to an increase in age. Changes in plasma prealbumin concentrations did not correlate with changes in plasma albumin as measured by the BCP method, but it did if measured by the ITM assay, although only for those with mild CRI. The differences between the groups might be expected, knowing that prealbumin concentrations are affected by the level of renal function and from this study, the BCP assay of plasma albumin did not

appear to be valid, assuming that the ITM assay was a valid gold standard. Studies in adults on haemodialysis, such as that by Chertow and colleagues (2000) have demonstrated that approximately 25% of the variation in plasma prealbumin can be explained by plasma albumin concentration, in keeping with the 18% observed in children with mild CRI in this study.

The results from this section have highlighted a number of concerns. Firstly, the two methods used for analysis of plasma albumin concentrations appear to be measuring albumin differently, explanations for which are not apparent. The present observations however, are in agreement with others, who found the BCP analysis gave lower values in children with severe CRI compared to immunoassay analysis (Wells et al, 1985; Carfray et al, 2000). Secondly, the presence of acute or chronic inflammation limits the specificity of both albumin and prealbumin as nutritional markers, the presence of which had not been quantified in this study by markers of inflammation, such as plasma C-reactive protein. Thirdly, the use of plasma prealbumin concentrations in children carries with it a number of confounding variables, including that of age, severity of CRI and the fact that a significant number of children reaching ESRD continue to possess residual renal function, facilitating degradation of plasma prealbumin, as highlighted by Duggan & Huffman (1998). For this reason, prealbumin is unlikely to be of use as a sensitive marker of nutritional status in children with milder forms of the disease, unless normal reference ranges for this group are developed with and without evidence of malnutrition. In conclusion, this study could not demonstrate the benefits of either plasma albumin or prealbumin as independent markers of nutritional status, with plasma albumin being most greatly influenced by the degree of proteinuria, and plasma prealbumin by age. A potential association between adequacy of protein intake and plasma albumin requires further investigation.

Chapter Eight

CONCLUSIONS AND RECOMMENDATIONS FOR FURTHER RESEARCH

Conclusions and recommended further research resulting from this study are discussed in relation to nutrients and specific clinical outcomes, in the same way as discussed in the introduction.

8.1 Estimation of glomerular filtration rate

Measurement of GFR continues to be used as the determinant of adequacy of kidney function in clinical practice. Accurate assessment of GFR is essential for correctly classifying children as having a degree of renal impairment or not, and for subsequently determining the frequency of monitoring and type of intervention required, particularly in those with mild CRI where clinical symptoms may not be evident.

Comparisons of cystatin C and creatinine/ height estimations of GFR with the gold standard [^{51}CR-EDTA] GFR, suggest that neither of these indirect methods are accurate enough to replace the radioisotope method for classifying children into the correct group of CRI, or correctly distinguishing those without renal failure from those with mild CRI. Frequently repeated EDTA GFR's however, would not be recommended in children due to the invasive nature of the procedure and repeated exposure to radiation. Either of the indirect methods would be suitable for interim estimations of GFR in children with a GFR below 100 ml/min/1.73m^2. Above that, the assay precision is less at low analyte concentrations. Comparisons between cystatin C and creatinine/ height show cystatin C to be moderately superior to creatinine/ height as a screening tool, exhibiting greater sensitivity at higher specificity as defined by ROC analysis, thereby reducing the proportion of children misclassified as having mild CRI or 'normal' renal function. On the other hand, from longitudinal comparisons between creatinine/ height and cystatin

C, the comparative lack of change in renal function as determined by cystatin C in those with moderate CRI, raises some concerns in using cystatin C as a tool for monitoring progression. This requires validation, with further research using greater numbers of children and a gold standard method to validate against. In the meantime, these results would not warrant a change in present practice of estimation of GFR using the creatinine/ height formula, with confirmation by an EDTA GFR in those suggested to have renal failure.

A cut-off EDTA GFR of 75 ml/min/1.73m^2 to identify those with and without CRI was used for the purposes of this study, whereas others refer to a GFR of 75% of normal as the cut-off, equivalent to 90 ml/min/1.73m^2. Findings from this study would suggest however, that optimum sensitivity and specificity were obtained at cut-offs of 80-85 ml/min/1.73m^2. In this study, a cut-off of 75 ml/min/1.73m^2 caused many children with mild CRI to be classified as normal. It would seem prudent to establish an agreed classification for future clinical practice and for comparisons of published research. One suggested method for doing this would be to design a relatively large study, comparing various endogenous markers for estimating GFR against a gold standard, and subsequently analysing the results using ROC plots and varying cut-offs, as attempted in this study.

8.2 Progression of CRI, proteinuria and blood pressure

Deterioration in renal function was modest in those with moderate and severe CRI, being of the order of 5 ml/min/1.73m^2 over the two year period. The mean reduction in GFR however, was 8.4 ml/min/1.73m^2 in those with mild CRI, despite this group containing the least number of children with proteinuria during the study period. If progression is assessed by movement of children from one category to the next over the two year period, 40-44% of children with mild CRI and 30% of children with moderate CRI moved into their neighbouring group, with one third of those with severe CRI developing ESRD. The fact that approximately 45% of children with mild CRI became classified as moderate CRI by the end of the two year study is perhaps surprising, and highlights the importance of being able to identify these children and the factors that may successfully delay their progression of CRI. The changes in GFR, estimated from the derived creatinine/ height model however, require validation against a gold standard

measurement, such as [^{51}Cr-EDTA]. The presence of proteinuria was greater with worsening severity of renal failure at baseline, but little change in the degree of proteinuria was observed during the study, despite an increase in the use of ACE inhibitors. An association between the degree of proteinuria and change in estimated GFR was apparent in those with moderate CRI. Concern was raised that those with moderate CRI had been under-treated with regard to an ACEI and other antihypertensives. In those with severe CRI, from a baseline comparison between those who did and did not complete the study, the mean urine protein: creatinine ratio was twice that in those failing to complete the study due to reaching ESRD, compared with those remaining. This supports the importance of attempting to reduce proteinuria to prevent progression, although a cause or effect relationship could not be determined.

Cross-sectional observations showed higher blood pressure with increasing severity of CRI, but whether this is cause or effect could not be established. An improvement in blood pressure over the two years was observed for the cohort as a whole, with the changes being greater for SBP than DBP. The least improvement in blood pressure was noted in children with moderate CRI, with an increase in DBP being observed, suggestive of under treatment with antihypertensive therapy in this group. Unlike other larger studies, changes in blood pressure during the two year period were not found to correlate with changes in GFR, which is more likely to be a result of sample size and use of discreet SDS data, rather than providing contradictory findings. Comparisons again between children with severe CRI who did and did not complete the study, revealed a mean SBP SDS in children reaching ESRD that was almost double that of those remaining in the study. Mean DBP SDS was also greater. An increase in sodium intake appeared to be associated with an increase in SBP in children with mild CRI and an increase in DBP in those with severe CRI.

The more rapid deterioration in GFR in children with mild CRI could not be attributed to proteinuria or blood pressure, although an increase in sodium intake was associated with a reduction in renal function and increase in SBP in this group. Further research would be warranted to determine whether sodium intake is an independent risk factor for deterioration of renal function, or whether it exerts its effects via increasing blood pressure and/ or proteinuria, using urinary sodium excretion to validate reported sodium intakes. In the meantime, it would seem appropriate to recommend restriction of

sodium intake as far as possible without resorting to the use of prescribable low salt products. Baseline sodium intakes were equivalent to that recommended for adults (100 mmol/d) in all groups of CRI, and adherence to 'no added salt' advice during the study proved to be difficult, particularly in children with mild CRI where sodium intakes increased disproportionately to energy intake. Families were able to stop the child concerned adding salt to food at the table, although many adults were unable to do so themselves, and a reduction in the use of gravies, soups and sauces was also achieved. Greater difficulty was associated with limiting intakes of crisps, tinned baked beans and spaghetti, sausages, beefburgers, and pizza which highlights the importance of manufacturers reducing the salt content of such processed foods, and the need for schools to increase their provision of healthier meals. Improved concordance to dietary advice may have been achieved in those with mild CRI if greater emphasis had been placed on the importance of salt restriction in this group as well as for children with more severe renal failure, by both medical and dietetic professionals.

Protein intakes reduced by 0.3 - 0.4 g/kg/day in all groups, although this reduction may be overestimated in children with mild CRI, who were suspected to be under-recording their dietary intakes. Unfortunately, comparisons with protein intakes estimated from 24 hour urea nitrogen excretion were not possible. The reduction in dairy products was associated with an increased contribution to total protein intake from meat and meat products, which was greatest in the first year. This was likely to reflect a moderate increase in meat intake during the first year, with a subsequent reduction during the second year, reflecting the stepwise approach required with dietary education. Greater protein restriction may have been possible if reviews could have been more frequent, in the order of 3-4 monthly, as opposed to 6 monthly in children with less severe renal failure. Resulting protein intakes remained above the 0.8-1.1 g/kg protein commonly used to assess the effects of protein restriction on progression of CRI in many children. Changes in growth did not appear to be related to changes in protein intake and no benefit was apparent in delaying the progression of CRI at the level of protein intake observed in the study. Unsurprisingly therefore, there were no apparent correlations between change in protein intake and changes in renal function or degree of proteinuria in this study. The potential detrimental association between low protein intakes and plasma albumin concentration as measured by the ITM method requires further investigation, to determine whether the current aims for protein intake in children with

CRI, which are equivalent to those for healthy children, are too low to maintain adequate nutritional status. Further research in children rather than adults with renal failure, with emphasis on assessment of nutritional status versus benefit from delaying progression of CRI following protein restriction is necessary, to establish guidelines for protein intake in children with CRI and whether they should differ depending on the severity of renal failure.

A decrease in dietary phosphate appeared to be associated with a reduction in progression of CRI in children with mild renal failure, and further research is warranted to explore this finding in a larger cohort of children with mild CRI, prescribed phosphate restricted diets. Unexpectedly, there was poor correlation between dietary protein and phosphate intakes. It is therefore important to attempt to distinguish between the role of the two nutrients in delaying the progression of CRI, as a reduction in phosphate may be more readily achieved without the need for specialised products, and is less likely to be detrimental to nutritional status and growth. Unfortunately, attempts to reduce dietary phosphate to below 1000 mg/d in children with mild CRI were less successful than in children with more severe renal failure, although this may result from the lack of importance of restriction in those with mild CRI perceived by both the families, and medical and dietetic staff concerned.

Attempts to prevent progression should occur as early as possible, and this study raises the questions as to whether restriction of dietary sodium and phosphate intakes in mild CRI are important as maintenance of normal blood pressure and absence of proteinuria in all children with CRI.

8.3 Growth, other anthropometrical indices and energy intake

Linear growth is one of the most important markers of clinical outcome in the management of children with CRI, and loss in height SDS appeared to be proportional to the severity of CRI. Baseline comparisons show deterioration in growth to start much earlier in the course of CRI than previously thought, with height being one of the most sensitive markers of impaired renal function. Height SDS improved over the two year period in those with severe CRI and was maintained in children with mild and

moderate CRI despite deterioration in renal failure, which could partly be attributed to the effects of a delayed pubertal growth spurt and/ or improved energy intake.

Unsupplemented energy intakes at baseline were lower with increasing severity of renal disease. A highly significant correlation between change in energy intake and change in height SDS in those with severe CRI was observed, with a 17% increase in EAR being required to promote a gain in height of 0.1 SDS. Findings from the study suggest the possibility that the change in energy intake rather than absolute energy intake is more important for the promotion of growth. This was only apparent in children with severe CRI, which may be due to the need for energy intakes to be suboptimal at the outset, as increasing an already adequate energy intake is not likely to improve growth. A relationship may also have been masked in children with less severe CRI, due to evidence of dietary under-reporting. The hypothesis that a change in energy intake is a greater determinant of change in height SDS than total energy intake requires further validation in a larger cohort of children, with future longitudinal research involving close dietetic monitoring and support, including maximising accuracy of completion of dietary diaries. Validation of reported food intake using 24 hour urine biological markers, and comparison of reported energy intake with estimated energy expenditure should form part of future methodology in this field of research. Attention should be paid to response set bias, which may occur with repeated use of food diaries in assessing the effects of dietary interventions.

Weight and MUAC SDS's were maintained in all groups of CRI, despite deterioration of renal function and advice to reduce weight and BMI SDS in some children with mild and moderate CRI. BMI SDS fell in those with severe CRI however, which was predominantly associated with an increase in height. Although MUAC SDS did not prove to be as sensitive a marker of nutritional status as BMI SDS in this study, anthropometric measurements should probably continue to involve a combination of MUAC and BMI for longitudinal comparisons, as unlike BMI, MUAC is independent of weight and height, and correlation between changes in the two variables over the two year period was poor. MUAC is age-dependent however, and hence should be used with caution for cross-sectional surveys of children who are small for their age. Skinfold thickness measurements are difficult to obtain in children, whereas MUAC is a cheap, reliable and reproducible measurement, less affected by fluid retention than

measurements involving body weight, such as BMI. For MUAC to remain valid, the reference data currently utilised are likely to require updating, which unfortunately was not undertaken at the same time as collation of the UK 90 growth reference data for weight, height and BMI. A macro for a spreadsheet of continuous reference data of SDS for MUAC, as produced for BMI SDS, would also be invaluable and should improve the sensitivity of this tool for research.

Maintenance of energy intakes incorporating use of oral nutritional supplements is difficult to achieve over a long period of time, and fortification of foods with additional fats and sugars does not appear to be sufficient to replace prescribed nutritional supplements. Consequently, those with moderate and severe CRI exhibited median reductions in energy intake during the study period. As improving energy intakes in those with suboptimal intakes appears to increase growth velocity, attempts should be made to introduce enteral tube feeding once failure to take oral nutritional supplements has been established, and before introduction of growth hormone, an expensive daily injection, is considered. The presence of a delayed pubertal growth spurt should also be considered via determination of bone age, before instigation of nutritional support measures or growth hormone therapy, based on poor growth for age. In those with severe CRI, where improvement in their renal function is unlikely, insertion of a gastrostomy button is more likely to achieve improved adherence to treatment, particularly in older children where passing a nasogastric tube daily can be quite traumatic. An increasing number of studies are demonstrating catch up growth without growth hormone in younger children, and further studies in older children are required.

8.4 Macronutrient intake and hyperlipidaemia

Increasing fats and sugars to maintain an adequate energy intake for growth are recommended in children whose appetites are suppressed, although this practice may be deleterious to cardiovascular health. A significant inverse correlation between fat and carbohydrate intake was observed, although intakes of starchy foods appeared to change little during the two year period. Children with severe CRI at baseline exhibited a raised total: HDL cholesterol ratio, although serum HDL cholesterol was above 1 mmol/l in the majority. Raised serum triglycerides were also seen with worsening severity of CRI at baseline, despite the samples being obtained in the non-fasted state.

Longitudinal comparisons of serum triglycerides however, did not produce any significant results, presumably because the samples were non-fasting; the potential variation over time being relatively small compared to the effects of food ingestion. Plasma HDL cholesterol concentrations significantly decreased over the two years in children with both mild and moderate CRI. The fact that an increase in sugar intake appeared to be associated with a reduction in plasma HDL cholesterol concentration in a number of children, would suggest that increasing energy intake should involve promotion of unsaturated fat rather than sugar, saturated fats being linked with an increase in total cholesterol concentration.

Recommendations for reducing saturated fat were successfully achieved without reducing total fat intake, via substitution of saturated fat spreads and oils with mono- and polyunsaturated products over the two year period. In contrast, increasing the total amount of fat and sugar added to foods in children not previously doing so, was not successful. Addition of cakes and biscuits, irrespective of their saturated fat content to the diet was encouraged, and successful in a number of children. Further research is required to determine whether this practice can continue, without exerting a substantial deleterious effect on lipids. Baseline intakes of sugar were high prior to dietary advice to incorporate additional sugar into the diets of children with poor appetites. Addition of sugar-containing drinks to the diet however, can be a successful way of increasing energy intake without compromising intake of foods, and without the need for prescription of a nutritional supplement, for which compliance is generally poorer. This may pose a problem for future dietetic practice, as equivalent non-protein containing drinks predominantly containing unsaturated fat are only available on prescription. Concordance with consumption of such prescribed products however, may be better than for glucose polymers, as they can be consumed in small quantities and taken as a medicine, twice a day. Such a proposal would be worth evaluation from a dietary compliance perspective, and for their subsequent effects on serum lipid profiles.

8.5 Bone metabolism, phosphorus and calcium intakes

Plasma phosphorus, alkaline phosphatase and PTH are the markers of bone activity currently used in clinical practice. Baseline plasma phosphorus concentrations were only elevated in children with severe CRI, although the majority in this group fell

within the normal reference range, which may have been associated with dietary phosphate restriction prior to the study. In contrast, baseline serum PTH concentrations were elevated in both those with moderate and severe CRI, indicating that serum PTH is a more sensitive marker of bone activity than plasma phosphorus. Nevertheless, the majority of children with moderate CRI exhibited PTH concentrations within the normal adult reference range, which would therefore not warrant treatment. This raises the question as to whether the adult reference range is appropriate for use in children, and studies should be done to confirm this. Plasma phosphate and PTH concentrations did not change significantly by the end of the two year period, although an increase in PTH occurred at one year, accompanied by an increase in the prescription of alfacalcidol in children with both moderate and severe CRI. There were concerns that poor concordance with alfacalcidol and phosphate binders was evident, particularly in relation to the older, adolescent children. Further work is required in clinical practice to find suitable approaches to improve concordance with treatment. More frequent monitoring and feedback may be helpful for some children, if distance from the unit is not prohibitive.

Dietary phosphate restriction to control hyperparathyroidism and subsequent renal osteodystrophy, and to prevent progression of CRI is primarily achieved via limiting dairy product intake in children, thereby reducing their intake of calcium. Children with severe CRI at baseline exhibited lower phosphate and calcium intakes as a result, this group having received dietetic advice prior to the study. The majority of children were able to reduce their intake of milk and other dairy products substantially by the end of the study period, resulting in dietary calcium intakes below 80% RNI in more than 50% of children with moderate and severe CRI. Despite a reduction of dairy products in those with mild CRI, they continued to consume greater quantities than those with more severe renal failure, such that all but one child had a calcium intake above 80% RNI. This may explain why 50% of those with mild CRI were unable to reduce their phosphate intake below 1000 mg/d, compared with 70 – 80% of children with moderate and severe CRI respectively.

A reduction in calcium intake was found to be associated with an increase in serum PTH concentrations in those with severe CRI, which resulted in an increase in the prescription of alfacalcidol in this group and in those with moderate CRI. This may not

have been necessary if their calcium intakes had been maintained. The majority of those with moderate CRI were not prescribed calcium carbonate, and the increase in PTH and subsequent prescription of alfacalcidol may otherwise not have been necessary in this group. If the findings linking progression of mild CRI with dietary phosphate prove to be valid from future work, then this group will also need to reduce their intake of dairy products to such an extent that a calcium supplement will be warranted. A randomised controlled trial of calcium supplementation (varying doses) versus no additional calcium as part of a phosphate restricted diet in children with varying levels of severity of CRI is required, to establish the importance of this treatment and the requirement for phosphate binders and vitamin D analogues in preventing the development of secondary hyperparathyroidism.

8.6 Anaemia and iron, folate and vitamin C intakes

Baseline dietary iron intakes were lower in children with severe CRI, with 50% having intakes below 80% RNI for iron. Dietary iron intakes did not significantly improve during the two year period, despite an increase in the number of children consuming fortified breakfast cereals and red meat. As a result, there was an increase in the prescription of oral iron in those with both moderate and severe CRI. It would appear that dietary manipulation of iron is unsuccessful in significantly improving iron status in these children. This may not be the case for those with mild CRI, whose haemoglobin concentration responded to a short course of oral iron and in which a few children were subsequently able to improve their dietary iron intake.

Dietary folate intakes reduced during the study period, which was likely to be associated with the apparent reduction in fruit and vegetable intakes. This would not have been recommended, although more emphasis would have been placed on incorporating higher energy containing snacks, which were likely to have been substituted for fruit. As a result, an increase in prescription of water soluble vitamin preparations was observed in those with moderate CRI, children with severe CRI already being in receipt of such a supplement. Vitamin C intakes however were seen to significantly improve during the study, despite the reduction in consumption of fruit and vegetables. This is likely to be associated with an increase in consumption of vitamin C rich drinks and maintenance of potato intake, the latter being the greatest contributor to vitamin C

intake. The prescribed micronutrient preparation also provides vitamin C, although the combined dosage is unlikely to exceed the quantity associated with increased risk of oxalosis. More children with mild CRI reported folate and vitamin C intakes above 100% RNI by the end of the study, which was associated with a reduction in children taking an OTC supplement during the study.

Manipulation of diet appeared to compromise the dietary adequacy of a number of nutrients, including calcium, iron (which is usually accompanied by zinc), and folate. Recognition of this is important, but should not negate such advice, as adequate energy, phosphate, sodium and possibly protein restriction seem to have a role in the prevention of progression of renal disease and development of renal osteodystrophy. Nevertheless, if such advice is to be given, compensation with prescription of a calcium supplement and appropriate micronutrient supplement consisting of water soluble vitamins, iron, copper and zinc preferably, would be indicated in the majority of cases. This raises the issue that in some children, there was a reluctance to prescribe such medications, due to the large number already being prescribed. This was a medical decision, whereas perhaps it should be one that is determined from consultation between both the patients and health professionals.

Haemoglobin concentrations were lower at baseline in children with severe CRI, with a haemoglobin below 10 g/dl in four children (21%), despite higher plasma ferritin concentrations, probably associated with prescribed oral iron. Unfortunately, the number of children with a haemoglobin < 10 g/dl increased to 54% of children with severe CRI by the end of the study, despite an increase in oral iron supplementation. Those with mild CRI exhibited an improvement in haemoglobin associated with short courses of oral iron therapy. Plasma ferritin concentrations increased during the study, with over 50% of those with severe CRI having concentrations above 100 μg/l, suggesting that their body iron stores improved, thereby supporting concordance with medication. Despite this, an increase in percentage hypochromic cells was observed in children with severe CRI, with 3 children demonstrating concentrations above 10%, indicative of functional iron deficiency. This may indicate that iv iron may have been more successful in correcting the renal anaemia in these children, but for others, prescription of rhuEPO may have been necessary. There appeared to be a reluctance to

prescribe rhuEPO in this study unit however, due to the perceived invasive nature of this treatment for children.

8.7 Summary

Children with mild CRI exhibited the greatest deterioration in renal function during the study, suggesting that attempts should be made to identify this group in clinical practice. As a screening tool for determining GFR, plasma cystatin C appears to be slightly more sensitive, but estimation of GFR by a creatinine/ height formula is comparable and if mild CRI is suggested, confirmation by a gold standard method is probably warranted. Assessment of nutritional status should involve a combination of markers, including height velocity or change in height SDS, BMI and probably MUAC, although the reference data for this requires updating, and plasma albumin if measured by an immunoassay method.

More frequent monitoring of children with moderate CRI may be necessary, to achieve normal blood pressure and minimise proteinuria to prevent progression of CRI. Restriction of dietary salt and phosphate intakes appear to be important in reducing the progression of renal disease in children with mild CRI particularly, but further studies are required to determine the extent to which these nutrients should be restricted. If the findings of this study are correct, dietary phosphate will need to be restricted and calcium supplementation will be necessary in all children with CRI. An adequate calcium supplement with phosphate restriction is also likely to help prevent early rises in serum PTH concentrations, but this also requires support from further research.

In those who have had suboptimal growth, catch up seems to be possible irrespective of age, if energy intake is increased by approximately 20% EAR, although this observation requires further investigation. Adequacy of protein intake also needs to be considered in relation to maintaining nutritional status and growth. Future consideration should be given to energy supplementation with concentrated unsaturated fat emulsions as opposed to glucose polymers, to prevent deterioration in plasma HDL cholesterol.

Protein and phosphate restrictions accompanied by an increase in energy dense foods, tend to result in suboptimal micronutrient intakes. Supplementation with calcium and a

micronutrient preparation consisting of water soluble vitamins and preferably iron, copper and zinc should be considered for every child, dependent on dietary diary analysis. Persistent renal anaemia was observed in children with severe CRI, where oral iron appeared to be insufficient, and in such instances iv iron and/ or rhuEPO should be considered.

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